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RHEUMATOLOGY

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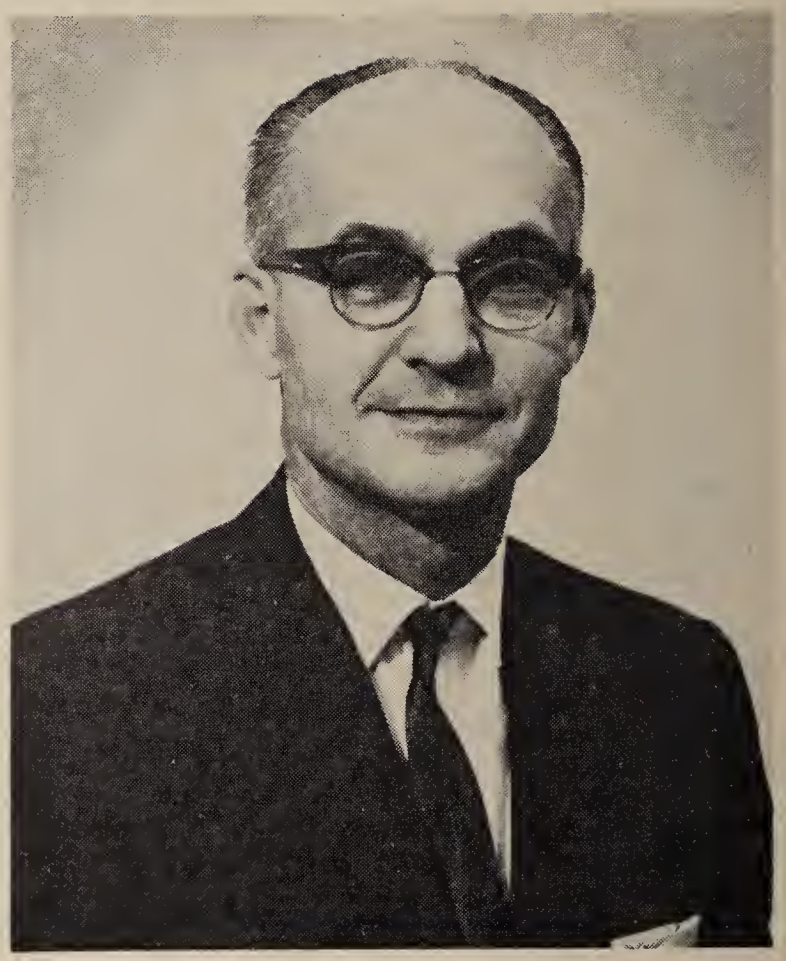
Guest Editorial

Rheumatology - The New Horizon



Dr. Ogryzlo received his M.D. from the University of Manitoba. During World War II as a Squadron Leader, he served as a Medical Consultant in the Royal Canadian Air Force. After three years of interneship interrupted by the war, in the Winnipeg General Hospital, Christie Street Hospital and the Toronto General Hospital, he served as Resident in Medicine in the Toronto General Hospital. In addition to serving as a Fellow In Neuropathology, he was among the first group of Research Fellows awarded by the National Research Council in 1946 and the first Research Fellow awarded by the Canadian Arthritis & Rheumatism Society in 1949. As a Research Associate of the Canadian Arthritis and Rheumatism Society, he has served on the staff of the Toronto General Hospital and Sunnybrook Hospital since 1952 and of the Wellesley Hospital since 1966. His research interests have largely involved the field of rheumatic diseases, especially the collagen diseases, pathogenesis and management of gout, metabolic effects of fasting, and the clinical significance of serum protein abnormalities in disease.

Arthritis is one of the oldest ills of man and its many faces have changed little over the centuries. Despite this ancient background it has until recently, remained one of the most neglected branches of medicine, largely because of its enigmatic character, relegated so to speak to the dungeons of progress while other fields were moving ahead with giant strides. The pervading view that virtually nothing was known about arthritis and less could be done for it, did little to stimulate interest in the field. It is not surprising therefore, that no attempt was made to distinguish between the many forms of rheumatic disorders until the turn of the century.

Then, in the short space of two score years, clear distinctions were drawn delineating such common forms of arthritis as gout, osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, Reiter's disease, psoriatic arthritis and the various collagen diseases, which formerly had all been lumped together under the name of chronic rheumatism. However, it is only during the last twenty years that rheumatology has begun to emerge as a new horizon, to the point where it has now assumed the position of one of the most exciting and rapidly progressing fields of medicine. Along with the malignant and cardiovascular diseases, rheumatology is undoubtedly destined to provide its share of spectacular advances in the health field, within the present generation. Thus far, the surface has only been scratched, opportunity beckons and the door is open to a monumental challenge for students with an enquiring and scientific mind.

Advances in the rheumatic diseases testify to the comprehensive scope of this new specialty, overlapping as it does the whole broad field of internal medicine. Few if any, of the many branches of medicine have escaped the impact of recent contribution to our understanding of these diseases. Who among us would question the significance of the discovery of the L.E. cell phenomenon and other immunologic phenomena encountered in systemic lupus erythematosus, in the present day concepts of autoimmune processes in a multiplicity of disease syndromes, in the production of tissue injury, or in the role of the immune mechanism in the field of homotransplantation. Can anyone doubt that the discovery of Rheumatoid Factor in the serum of patients with rheumatoid arthritis, while it has yet failed to reveal the

cause of the disease, nevertheless did attract many of our best scientific minds to study the serum proteins, thus contributing to the vast new knowledge of protein structure and function. Has any aspect of medicine not been touched by the discovery of the action of corticosteroid hormones on the mechanisms involved in hypersensitivity and inflammation. What is more dramatic than the ability to control the enzymatic production of uric acid in diseases such as gout, or the myeloproliferative disorders. These are but few of the contributions of rheumatology, more are in the offing.

Nor have the individual patients who suffer from the more serious forms of arthritis been forgotten, despite the lack of curative treatment for these diseases. The intelligent application of well established principles of physiotherapy and rehabilitation have been shown to do much to control these diseases and minimize the serious disability that formerly resulted from neglect. This has best been illustrated by the results attained with intensive treatment provided to arthritis victims in the segregated setting of Rheumatic Disease Units, newly created in a number of University Teaching Hospitals. A declared objective of the Canadian Arthritis & Rheumatism Society as far back as 1949, such centres are only now coming into being in North America. In addition to providing exemplary care for patients, these Units also provide an ideal setting for both undergraduate and graduate education, not to mention the increased facility to conduct both basic and clinical research in this important field.

METRO A. OGRYZLO, M.D., F.R.C.P. (C)
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Editorial

A National Health survey in 1957 revealed that over 10,000,000 people of all ages in the U.S. had complaints of the arthritic and rheumatic type. Although this figure indicates the tremendous incidence of arthritic diseases, the student unfortunately seldom has the opportunity of being exposed to them clinically. There are several reasons:

(1) The more common afflictions, such as rheumatoid arthritis, are more often treated by the general practitioner or on an out-patient basis, and consequently are not available for teaching purposes.

(2) Disorders such as disseminated lupus erythematosus, scleroderma, and polyarteritis nodosa, are quite rare; a student may attend clinics in hospitals for two years and never see a good representative case.

(3) It was found in 1957 that 20% of the people with arthritic complaints never seek medical treatment of any kind.

Therefore, it is the purpose of this journal to draw attention to an area with which the practitioner must be familiar, but which he may not be subjected to clinically until his practice actually begins.

In addition, the editors wish to stress the tremendous role that immunology is playing in the advancements of both rheumatology and of medicine in general. Accordingly, we feel that this interesting and important subject should be presented in the new curriculum with appropriate emphasis.

B.R.T. R.A.B.

Etiology And Clinico-pathological Features Of Rheumatoid Arthritis

B. R. Taylor 6T8

Rheumatoid arthritis (RA) is worthy of intensive study not only because it affects nearly 4% of the adult population, and one half of those severely, but also because its etiology remains obscure. Like the other collagen diseases, RA is a generalized inflammatory disorder; however, unlike the others, it affects the articular system predominantly. The subject to be discussed here is adult RA, but at the conclusion of the article, a brief outline of the principal differences between the adult and juvenile forms of the disease will be given.

EPIDEMIOLOGY

The incidence of RA increases in middle age, with one peak of frequency of onset at 35 years, and another at 45 years.[1] At these ages, women are affected two and one half times as often as men, but in old age, the sex incidence is equalized. The disease is seen more frequently in damp, cold, temperate climates, and its onset has a predilection for the month of March, even though it can occur at any time. Recent investigations have shown a slightly greater tendency to the acquisition of the disease in subjects possessing the Rh positive and Type B blood groups.[2] RA used to be thought to occur in patients of ectomorphic habitus, but this is now believed to be a result of, rather than a predisposition to, the disorder.

AETIOLOGY

Theories on the etiology of RA, involving such diverse topics as nutritional deficiency, metabolic abnormalities, endocrine deficiencies, and mental aberrations, have been probed with no definite conclusions. Even though trauma, in the form of injury, strain, infection, or surgery, has been recognized as a predisposing factor, it has not been considered as an etiological contributor. At present, interest revolves about three main possibilities:

(1) Auto-immunity
(2) Infection
(3) Heredity

(1) Auto-immunity

Approximately 75% of the sera of RA patients contain a Macroglobulin (IgM) called Rheumatoid Factor (RF), which reacts with denatured 7s gammaglobulin (IgG). Produced in large pale cells and plasma cells in the lymphoid follicles, RF can actually consist of aggregates of 7s IgG, (producing for example a 13s protein), in addition to the more common 19s IgM form. In fact, some believe that different lymphoid follicles are capable of producing different rheumatoid factors. The macroglobulin, in precipitating denatured 7s IgG, produces an unusual 22s aggregate. (see Fig. 1.)

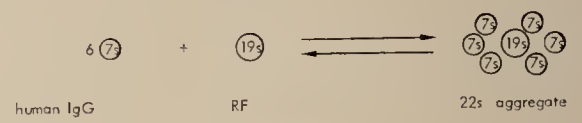

FIG. 1.

In various studies, a strong correlation has been shown between the level of RF in the serum, and both the severity of the clinical picture, and the likelihood of serious complications of RA. Many theories have been proposed to implicate RF aetiologically; one of these is the auto-immune theory which has enjoyed much exposure in the last decade. It states that some sustained antigenic stimulus, as yet undiscovered, promotes formation of a specific antibody which reacts with the antigen to form immune complexes. The consequent alteration of the host's gammaglobulin 'by immune complex formation, provides the stimulus for production of autoantibodies, (in this case rheumatoid factors), which combine with the complexes to produce tissue destruction, supposedly via leucocyte phagocytosis and resultant lysosomal enzyme release, as discussed in a following article. The fact that RF is also present, at lower levels, in sera of some patients with SBE, leprosy, TB, and syphilis, may lend support to the immune hypothesis, since these diseases certainly involve chronic immune stimulation. Two facts, however, point away from this theory: the antigen has never been identified, even though various drugs and chemicals have been considered; patients with agammaglobulinemia (AGG), may get the disease, even though their ability to manufacture gammaglobulin is impaired.

(2) Infection

The Infection Theory has been investigated for decades, first as one concerning a "focal infection", and more recently as one involving a less specific infectious process. Nebulous associations do exist between the arthritides and certain infections. For example, arthritis often accompanies microbial diseases such as rubella and Reiter's syndrome, and in addition, the articular symptoms of RA are occasionally preceded by a flu-like syndrome. However, this is not enough to assume a cause-effect relationship.

Interest now centres around PPLO or Mycoplasma, an organism, neither virus nor bacterium, which has

lately been isolated by certain workers[3] from the synovial fluid of RA patients. The Bedsonia group, (Psittacosis, Ornithosis, L.G.V.) is also being examined. It is thought that perhaps PPLO or another organism is the sustained antigenic stimulus referred to in the immune theory, necessary to cause derangement of the body's formation of antibodies. The problem with this hypothesis is that no "infection" has ever been reproduced in an experimental subject, (by serum, synovial fluid, or subcutaneous nodule transfer from an affected individual) and no organism has been as yet regularly isolated.

(3) Heredity

Investigations have shown that a hereditary factor does exist, for offspring of two RA patients have 6 times the chance of being affected as those of control subjects. If only one parent is affected, the incidence of RA in the children is twice that of the normal population. The exact definition of this factor, however, is lacking.

Agammaglobulinemics acquire RA up to 8 times as often as those with intact immune responses, and it is with this fact in mind that the following question is posed; "might there be in RA subjects the incomplete expression of a genetic defect in the immune response which, in the complete form, is expressed as agammaglobulinemia?" [4] In other words, there may exist a genetically determined anti-RA factor which is ineffective in AGG and only partially effective in RA patients. In addition, since AGG's are extremely susceptible to infection, does the fact that they have RA often, not support the theory that infection plays a role? This is a possibility, but it must be noted noted that while bacterial infection often produces death in AGG, viral infections are combatted far better.

Many other questions, such as the association of RA with Hashimoto's disease, and the presence of remission during pregnancy and jaundice, remain unanswered.

COURSE

RA can have either a sustained or an episodic course, both of which are extremely difficult to predict. One case may last for weeks, another for 30 years. The disease never kills a patient per se, but in general is said to reduce longevity by about 5 years, and may be complicated by much more systemically serious illnesses such as necrotizing arteritis, SLE, or secondary amyloidosis. The course may very roughly be predicted by the level of RF in the serum; if the level is high early in the disease, or is sustained over a long period, the hope of a lengthy remission is scant; if an exacerbation of clinical symptoms and RF elevation lasts 3 years, a subsequent remission is unlikely.

THE A.R.A. CLASSIFICATION

Since the pathological features, clinical manifestations, and laboratory findings of RA may be reviewed in any text, they will be outlined here in association with the eleven criteria for the diagnosis of RA described by the American Rheumatic Association in 1958. These criteria were originally established in order to help standardize diagnosis of the disease throughout the continent, so that the numerous studies being undertaken would be more meaningful to all physicians:

1. Typical pathology.
2. Pain or tenderness in at least one joint.
3. Symptoms in at least one other joint.
4. Swelling around joints.
5. Symmetrical joint swelling.
6. Morning stiffness.
7. Subcutaneous nodules.
8. Characteristic histological changes in nodules.
9. Positive SCAT (Sheep Cell Agglutination Test).
10. Poor mucin precipitate from synovial fluid.
11. Typical X-ray changes.

The employment of this diagnostic method labels cases of RA according to Table 1.

Table 1.
THE DIAGNOSIS OF RHEUMATOID ARTHRITIS

	No. of criteria satisfied	*Duration of symptoms*
Classical RA	7	6 weeks
Probable RA	5	6 weeks
Possible RA	3	4 weeks

An explanation or enlargement of the criteria as stated above will be given.

1. The original lesion in the synovial membrane is one of congestion, gradually evolving into a marked villous hypertrophy with the production of inflammatory granulation tissue. This tissue spreads to cover articular cartilage, (where it is called *pannus*) and also invades subchondral bone, producing cysts and pseudocysts. Fibrous, hyaline, or bony ankylosis may eventually occur in consequence of metaplasia of the pannus and formation of fibrous tissue across the joint space.

2. The initial complaints are usually pain and tenderness in at least one joint, even though an indistinct prodome of general malaise and fatigue may antedate the articular symptoms. The joints first affected are often the proximal interphalangeals (PIP), of the hand, the metacarpophalangeals (MCP - especially 2nd and 3rd) the metatarsophalangeals (MTP - especially 2nd, 3rd and 4th) and the wrist; however, in some cases, more subtle presentations, such as swelling of the extensor carpi ulnaris or achilles tendons near their insertions, may be seen.

3. More than one joint may be involved. In fact, eventually, any of the knee, elbow, ankle, shoulder, hip, sterno-clavicular, temporomandibular or crico-arytenoid joints (in decreasing order of frequency) may give symptoms. In addition, studies have shown that the cervical spine is more often involved than was previously thought.

4. Swelling, because of soft tissue thickening and/or exudative fluid, may be evident around the affected joint, and is best demonstrated in the fusiform, spindle-shaped fingers, or the swollen fluid-containing knee. These early deformities may be followed eventually by more serious ones such as ulnar deviation and flexion contractures; the former is caused by:

(i) inflammatory destruction of bone and joint under the influence of muscle pull, causing subluxation at the MCP joints.
(ii) weakening of capsule and ligaments
(iii) tendon contractures and ruptures

Flexion contractures are due to involuntary splinting of a painful joint, with the stronger muscle groups (flexor groups in the upper limb) prevailing, followed by ankylosis in the flexed position.

5. Symmetrical involvement eventually develops, as the same joint on both sides of the body will be affected.

6. Morning stiffness, or stiffness after any inactivity (gelling), is often marked; the more prolonged and refractory the stiffness each morning, the more advanced the disease process.

7. In 25% of classical cases, firm, mobile, non-tender masses averaging one centimetre in diameter are found on pressure points such as the extensor aspect of the forearm below the elbow, the scapula, buttocks, patella, or scalp. These are called subcutaneous nodules, and are thought to result from ischemia produced by both pressure and an associated arteritis.

8. These nodules, pathologically speaking, are non-encapsulated, and possess three zones on microscopic examination;

(i) a central area of necrosis
(ii) a surrounding pallisade of macrophage-like cells
(iii) an enveloping layer of granulation tissue with chronic inflammatory cells

9. The SCAT for RF is usually, but not always, positive. The patient's serum is added in serial dilutions to sheep cells which have been sensitized with rabbit serum containing anti-sheep erythrocyte antibodies. The subsequent agglutination is considered positive at a dilution of 1/32. This test is more specific than the commonly used latex fixation test (LFT) which employs the same principle, except that inert latex particles are coated by denatured human gammaglobulin and titrated with serial dilutions of serum.

10. There may be a poor "mucin precipitate" from synovial fluid. In this test, acetic acid is added to synovial fluid, and if the content of albumin and hyaluronate is low, a loose, easily fragmented clot forms. The synovial fluid of a normal individual on the other hand, contains adequate albumin and hyaluronate, and a tight precipitate results.

11. In recent studies,[5] the feet have been shown to be affected before the hand radiologically at least, in a substantial number of cases. In general however, the following X-ray changes are seen:

(i) periarticular soft tissue swelling, especially in the wrist, PIP and MCP joints
(ii) narrowed joint space, due to the articular cartilage destruction and replacement
(iii) periosteal elevation with ossification
(iv) either local or generalized demineralization with coarse trabeculation and narrow cortex (especially in the MCP, PIP, wrist, MTP joints) occasionally with pseudocyst formation
(v) deformities in hands and feet (in the latter the 2nd - 5th proximal phalanges turned dorsolaterally on heads of metatarsals with IP's flexed)
(vi) destruction of cartilage with fibrous replacement, producing fibrous or bony ankylosis.

There is of course good correlation between severity of the X-ray picture and the disease activity.

OTHER CLINICO-PATHOLOGICAL FEATURES

General

A fever, when present, is invariably low grade, and may be associated with a tachycardia. It has often been attributed to iatrogenic causes i.e. steroid withdrawal. A distinct weight loss is evident in most cases, due not only to the chronicity of the inflammatory process, but also in some patients to depression which inhibits their appetites. It is not surprising that mental difficulties do develop, as the disease may labour on for 20 years, producing severe physical debility.

Muscle

Accompanying the joint problems are often profound muscular weakness and atrophy, more marked than the activity of the disease might warrant. In fact, on microscopic examination, disuse atrophy and evidence of diffuse chronic inflammation are seen. The striking degree of wasting in the interosseous spaces of the dorsum of the hand is clear testimony of muscular involvement.

Arteries and Skin

Also present in the clinical picture of RA are erythematous palms, and cold, clammy, atrophic, bronzed skin, the latter being evidence of a vasomotor instability ap-

TABLE 2.
Differences between adult and juvenile RA[6]

FEATURE	*JUVENILE RA*	*ADULT RA*
1. Systemic findings		
—high fever (102 - 106°)	—common (25%)	—uncommon (1%)
—rash	—common (25%)	—uncommon (2%)
—chronic iridocyclitis	—common (25%)	—uncommon (1%)
2. Natural history of onset	¼-acute onset with fever, rash ½ polyarticular ¼ monoarticular	pain+/or tenderness in at least one joint
3. Non-articular features		
—subcutaneous nodules	6%	20%
—abnormalities of growth	50%	Not applicable
4. Laboratory findings		
—leucocytosis (>12000)	50%	25%
—+RF test	10 - 30%	65 - 85%

parently caused by the associated chronic inflammatory process in small arteries; even leg ulcers may develop. The arteritis varies from a non-necrotizing type to one similar to that seen in polyarteritis nodosa, and steroid therapy is still considered to be a factor in its aetiology. The blood supply to peripheral nerves may also be affected, resulting in peripheral neuropathy.

Lymphoid Tissue

In about 50% of cases, a generalized lymphoid hyperplasia manifested by splenomegaly and enlarged nodes is seen, presumably because of the chronic immune stimulation. This generalized involvement often leads to a mistaken diagnosis of a lymphoma.

Tendons

Tendon sheaths may be involved by either a non-specific or a specific inflammation; the latter can produce focal fibrinoid necrosis and possible rupture or tenosynovitis.

Eye

The eye is affected in up to 45% of cases, in the form of episcleritis, uveitis, keratoconjunctivitis sicca, or posterior subcapsular cataracts. Necrosis of the sclera (after chronic inflammatory cell infiltration) is responsible for the episcleritis, and, if this process creates focal softening of the eye wall (scleromalacia), uveal tissue may herniate through the defect.

Heart

Rheumatoid heart disease manifests itself in a subclinical pericarditis in almost all cases, and valvular insufficiency, heart block, and cardiac failure in some. Granuloma-like lesions occur in the valve leaflets and rings and the myocardium, explaining the symptoms and signs.

Lung

Three pulmonary conditions sometimes attributed to RA are:

(1) Silicosis-like nodules in coal miners who have RA (Caplan's Syndrome)

(2) Nodules in lung resembling subcutaneous nodules

(3) Idiopathic interstitial pneumonia

However, these are uncommon findings, and certainly not conclusive evidence of an association with RA.

LABORATORY FINDINGS

Blood

(1) *Anemia*

A normocytic, normochromic anemia which is refractory to Iron, B12, and folic acid, is produced. Several factors may be responsible: a mild extracorpuscular hemolytic element, some degree of bone marrow aplasia, and iron deficiency from long term salicylate therapy with chronic bleeding into the gut. The serum iron is low, but transferrin levels, and therefore iron uptake, are *normal*.

(2) *Leucocytes*

The leucocyte count is usually normal, but may be increased during an exacerbation, or after chronic administration of steroids has caused bone marrow stimulation.

(3) *ESR*

The ESR is a valuable index of disease activity; its elevation during exacerbation is caused by increased production of fibrinogen and α_2-globulin. However, even in remission the globulins may still remain elevated,

and in consequence, the ESR. The C-reactive protein, which is also a non-specific response to inflammation, parallels the ESR in RA.

(4) *Serum proteins*

As was stated earlier, unknown antigens may stimulate antibody production in RA, and as a result, the γ-globulin is elevated along with α_2-globulin and fibrinogen. The fact that albumin levels are decreased has only recently been explained, i.e. that albumin is broken down to a greater extent in the hypermetabolic state of RA.

Amino acids

One of the present mysteries is the increased excretion of tryptophan metabolites in RA patients, namely 3-OH anthranilic acid. There has accordingly been postulated the existence of a preferential shunt of tryptophan metabolism into the kynurenine pathway via the enzyme tryptophan pyrrolase. This theory has not yet been widely accepted.

Serological tests

(1) *Rheumatoid factor*

RF is measured in two ways, the SCAT in which a 1/32 titre is considered positive, and the LFT in which a 1/160 titre is positive. These tests are positive in approximately 75% of cases of classical RA, and virtually all those with subcutaneous nodules.

(2) *LE cell phenomenon*

A positive result of this test, like a high serum level of RF, is indicative of more serious disease, and greater frequency of complications. Basically, certain γ-globulins, (LE cell factors) which are auto-antibodies against the nuclei of leucocytes, penetrate the nuclear membrane, causing eventual cell deterioration and the extrusion of the altered nucleus. Normal leucocytes phagocytose this free particle, and the new cell containing the damaged nucleus is called an LE cell.

It is seen in 100% of SLE patients, but only 15% of cases of RA. The anti-nuclear factors are of the 7s IgG group in SLE, but are macro-globulins in RA, demonstrable through serological testing in 25% of cases.

(3) *Liver function tests*

Due to the alteration of albumins and globulins in RA, those liver function tests which reflect hepatic association with the serum proteins are, as one would expect, abnormal. The A/G ratio may be reversed, and the CCF and TT positive in many instances.

(4) *Renal function tests*

The kidneys are not affected unless secondary amyloidosis develops in the later stages, in which case asymptomatic proteinuria, or clinical and laboratory evidence of the nephrotic syndrome may present.

SUMMARY

In this article, an attempt has been made to incorporate contemporary ideas about adult RA into a discussion in which pathology explains clinical presentation. A brief chart outlining the basic differences between this entity and juvenile RA (Still's disease) may be useful to the student. (see Table 2.)

ACKNOWLEDGEMENT

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BIBLIOGRAPHY

1. Hollander.J. L.: Arthritis and Allied Conditions, 7th Ed. 1966.
2. Stoia, I. et al: "Blood groups ABO and Rh+ factor in Rheumatic Disease", Annals of the Rheumatic Diseases, July 1967.
3. Bartholomew et al: Arthritis and Rheumatism, Vol. 8, p. 376, 1965.
4. Christian, C. L.: "Etiologic considerations of RA", A. and R., Vol. 7, No. 5, Oct. 1964.
5. Thould et al: A.R.D., p. 220, May, 1966.
6. Calabro and Marchesano: Juvenile RA, NEJM, Vol. 227, No. 13, Sept. 28, 1967.

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The Treatment Of Rheumatoid Arthritis

R. A. Bear 6T8

INTRODUCTION

Rheumatoid Arthritis might well be considered a 'total involvement' disease. This is certainly true of the unfortunate patient with his multitudinous complaints; it must also be true of the doctor, be he scientist or clinician. With the former rests the challenge of discovering the aetiology of this disorder. The latter has a wide variety of facilities, techniques and medications at his disposal, and these must be coupled with patience and understanding, and continually adapted to the changing needs of the patient.

With Rheumatoid Arthritis, the basic therapeutic regime combines rest, salicylates and physical therapy. In this review, this basic programme will be discussed and the various methods which are helpful adjuncts to this therapy will then be described.

THE BASIC REGIME

(A) Rest

Rest is *the* most basic necessity and includes systemic, articular and emotional rest.

In severe acute disease, systemic rest is achieved by complete confinement to bed and this is best carried out in hospital, if the home situation is lacking. The patient with mild active disease must rest two to four hours during each day. Initially, he may complain of joint and muscle stiffness (gelling) after this period of inactivity, but this phenomenon disappears in time. The rest programme may be liberalized as a remission occurs.

Articular rest is accomplished as follows:

1. Rest splinting: to relieve pain and prevent deformity.

2. Corrective splinting: to correct deformity.

3. Functional static bracing: to maintain correction of deformities.

4. Functional dynamic bracing: to maintain correction of deformity, and to assist movements by elastic, spring or motorized elements.

Rest splinting will be discussed here.

Flexion of painful, inflammed joints helps to relieve the discomfort. Thus patients develop a tendency to keep the involved joints flexed and this, combined with irritative muscle spasm, leads to contracture formation. Rest splinting avoids this by reducing the spasm and mechanically preventing contractures.

Partridge and Duthie[1] have demonstrated that in severe acute disease, absolute bed rest and joint fixation by casts for four weeks can be safely employed, resulting in relief of pain, reduction in disease actvity, and an overall tendency towards increase in joint motion. Despite these claims, most rheumatologists insist upon removal of splints and passive or active movements of joints through their widest possible ranges, several times each day.

Consider the M.C.P. joints of the hand. During acute rheumatoid inflammation, these joints swell and the articular capsules stretch, resulting in joint instability. Muscle spasm and pain lead to flexion deformities which eventually progress to subluxation and eventually to severe ulnar deviation. To prevent these changes, a plastic cuff moulded firmly about the M.C.P. joints is utilized. It is held on by a Velcroe band and can be easily removed while the joints are exercised.

Metatarsal bars are also widely employed. These are supports which fit in the sole of the shoe just behind the painful metatarsal heads and they relieve these bony structures of their major role in weight bearing, thus enabling early ambulation of the patient.

Emotional rest must also be attained. The disease process with the limitations it imposes must be patiently explained. Tranquilizers, anti-depressants and muscle relaxants are frequently indicated.

(B) Physical and Occupational Therapy

Physical therapy includes exercise, heat application, massage and occupational therapy.

Proper exercise, as previously discussed, prevents deformity and helps to maintain adequate ranges of movement. In addition, circulation and metabolism are increased, thereby improving muscle bulk and strength.

Passive exercises are utilized in the acute stage, and as joint inflammation subsides, *assistive* (patient helped by therapist), *active*, and *resistive—active* (exercise against force) exercises are used. Procedures must be carefully explained to the patient who should be encouraged and frequently re-evaluated.

Hydrotherapy is of special importance, post-operatively or when the patient has large joint involvement. In water, movement is possible in all planes without gravitational loads. Thus, a patient with hip or knee inflammation (or after recent surgery to those joints) may walk in the water without severe pain, and without inducing further injury to these weight bearing joints.

Heat may be administered by methods of conduction (hot baths, hot water bottle, paraffin baths), conversion (long or short-wave diathermy, microwave) or radiation (infrared lamps). Heat increases the blood

supply to muscles and results in analgesia by muscle relaxation and a sedative effect. Hot water bottles and temperature-controlled hot baths are simple measures which can be used in the home. Whirlpool baths combine the effects of heat and massage. Hot paraffin baths are used to apply heat to the extremities. They are applied locally as gloves or casts, and are peeled off after 30 - 60 minutes. The more complicated methods of heat application must be used with discretion, and under competent supervision.

Massage induces muscular relaxation and vasodilatation by release of histamine-like substances. After systemic massage, discomfort is frequently lessened and a sedative effect is achieved. In Rheumatoid Arthritis, especially in the aged, massage may be used as a partial substitute for exercise.

Occupational therapy includes any prescribed mental or physical activity which aids in recovery or renders convalescence more pleasant. Advantages to be gained include mood elevation, increased muscle power and range of movement, and decreased apprehension regarding prognosis.

(C) Salicylates

In addition to being inexpensive and relatively non-toxic, A.S.A. is by far the most effective therapeutic agent in the treatment of Rheumatoid Arthritis. In small doses it acts directly on the hypothalamus to raise the threshold to somatic-type pain. In larger doses it exerts anti-inflammatory effects by diffusing into the synovial fluid and inhibiting catalytic enzymes and kinins. Furthermore, A.S.A. has been shown to partially protect experimentally traumatized cartilage[2].

There are few serious side effects to salicylate therapy. Tinnitus occurs at high serum levels and may be used as a guide to dosage. Adults are given 10 - 15 grains q.3.h while awake and if tinnitus occurs, the daily dosage is decreased by 10 - 15 grains until a tolerable dose is achieved. A.S.A. should be given on a regular schedule and ought not to be given p.r.n. Serum salicylate levels should be monitored and kept close to 20 mg. %.

Gastric irritation with A.S.A. is sometimes a problem. Although the first enteric-coated agents resulted in unreliable absorption, newer preparations are more effective. However, expense is a consideration in their use.

(D) Nutrition

Although the anaemia of Rheumatoid Arthritis does not respond to hematinic agents, iron-deficiency anaemia may result from gastro-intestinal bleeding caused by drugs and medicinal iron may be required.

No food idiosyncrasies have been implicated in Rheumatoid Arthritis and the values of a well balanced diet are obvious.

ANCILLARY METHODS IN TREATMENT OF RHEUMATOID ARTHRITIS

(A) Drugs Used in Treatment of Rheumatoid Arthritis

Many rheumatologists presently utilize combination therapy in the treatment of Rheumatoid Arthritis. If salicylates are ineffective in controlling pain and inflammation, phenylbutazone (Butazolidin), oxyphenbutazone (Tandearil) or indomethacin (Indocin) is given along with A.S.A. This regime is continued for 1 - 4 weeks, and if little benefit is noted, gold salts (Solganal) or antimalarials (Aralen) are added. The patient is then followed for an additional 4-6 months, after which time a further assessment is made. If a remission still has not occurred, systemic steroids are administered, either alone or in conjunction with the other agents. It is to be stressed that systemic steroid therapy is absolutely a last resort. Finally, some antineoplastic agents are being studied on an experimental basis (e.g. cyclophosphamide).

The therapeutic pharmacology of A.S.A. has been previously outlined. Each of the other agents will now be described briefly.

Phenylbutazone (P.B.Z.) is a pyrazol derivative whose mechanism of action is unknown. The initial dose is 100 mg. b.i.d. and this may be increased to 600 mg. daily. Water retention, GI irritation, dermatitis, hepatitis, renal damage and blood dyscrasias may occur. Another important side effect is the potentiation of both coumadin derivatives and sulfonylureas. Bleeding may be precipitated by the former, and hypoglycemia by the latter. Congestive heart failure, blood dyscrasias and peptic ulcer are contra-indications to the use of P.B.Z.

Oxyphenbutazone is a derivative of P.B.Z. which is equally effective, and can be taken by patients intolerant of P.B.Z.

Indomethacin is an indene derivative with anti-inflammatory effects of obscure origin. It is available in capsules of 25 mg. and one capsule is taken with each meal initially; this dosage may be slowly increased to 150 mg. per day. Ulcerogenesis, headache, vertigo, nausea and vomiting and depression may occur. This agent should be avoided in those with a history of peptic ulcer.

Gold salts are usually administered I.M., 10 mg. the first week, 25 mg. for the next two weeks and 50 mg. weekly until the twentieth week. If a positive therapeutic effect is achieved, low maintenance doses are continued for many months, for example: 50 mg. I.M. every three weeks. The beneficial effects of this agent are directly related to stores of gold in the body and relapses are common when administration is stopped. Skin eruptions occur and may lead to severe exfoliative dermatitis. Leukopenia, agranulocytosis, thrombocyto-

penic purpura, proteinuria, jaundice, stomatitis, diarrhea and proctitis are the common toxic effects. Gold should not be administered in the presence of skin disease, renal disease, hepatic dysfunction or blood dyscrasias. During therapy, frequent examinations, urinalyses and white blood cell counts must be performed. If severe toxic reactions should occur, dimercaprol (B.A.L.), penicillamine or steroids may be used.

Chloroquine exerts encouraging anti-inflammatory effects, but the incidence of side effects is high. Pruritic rashes, headache, nausea and vomiting and leukopenia may occur. Visual disturbances of a reversible nature occur by deposition of the drug in the cornea. In addition, a toxic retinopathy sometimes occurs, which can result in permanent blindness. Frequent eye examinations must be performed on these patients. Chloroquine is usually given as 250 mg. daily. The only positive contra-indication is previous severe toxicity.

The mechanism of action of the *systemic steroids* is described elsewhere in this journal. These agents are used as a last resort, and in the lowest possible dosages. It is advisable to start with a low dosage and slowly increase it as required; if patients are begun on high doses they may feel so much better that they will complain bitterly when their dosages are decreased to less toxic amounts. Toxic effects include skin changes, ulcerogenesis, endocrine abnormalities (impotence, hirsutism, amenorrhea), osteoporosis, increased incidence of myocardial infarction (hypertension + polycythaemia), diabetogenesis, difficulty in controlling infection, iatrogenic Cushing's Syndrome, and withdrawal syndrome. Acute adrenal insufficiency may be precipitated in patients on prolonged systemic steroid therapy by conditions of stress. These agents are contra-indicated or should be used with great caution in the presence of peptic ulcer, osteoporosis, thromboembolic phenomena, uncontrolled infection, diabetes, pregnancy, cardio-vascular or renal disease, psychosis or psychoneurosis.

(B) Intrasynovial Steroid Injection

Intrasynovial steroid injection is indicated when one or a few peripheral joints are affected and specific infection has been excluded. Even in the presence of generalized, low-grade joint involvement, injection of steroids may be used to relieve one or two acutely inflammed joints. Joints resistant to systemic drug therapy are frequently injected with satisfactory results.

Infection in the joint is a contra-indication, as is severe generalized joint involvement. The procedure is avoided when there is severe osteoporosis around the joint, when the joint has no articular space or when injection has been without benefit in the past.

The steroid compound is apparently taken up by the cells of the synovial fluid and membrane and symptomatic improvement occurs in 24 hours. Maximal benefits are noted within three days. Best results are obtained with prednisolone-t-butyl-acetate, and the improvement usually lasts for months.

Side effects with this procedure include excacerbation of inflammation, weakness of the injected extremity, joint infection, over-use of an improved joint (which should be rested), and production of a Charcot joint by repeated injection.

(C) Surgery in Rheumatoid Arthritis

Surgery in no way provides a cure for Rheumatoid Arthritis, but is directed toward relief of pain and correction of disability, painful or otherwise. Each patient is assessed individually on the basis of occupational potential, social environment and emotional constitution as well as on the basis of the surgical problem *per se*.

Pre-operative exercises are employed to build up muscles surrounding the affected joint and to teach the patient exercises which will be required post-operatively. Joint inflammation is not a contraindication to surgery, but patients who have been bedridden for lengthy periods of time are poor operative risks as are those on long-term, systemic steroid therapy. Care must be exercised when operating on patients with peripheral vascular disease and atrophic skin. After the procedure, rapid mobilization of the joint must be ensured. Hydrotherapy and muscle setting exercises are used in the early post-operative course.

Of the procedures available, *skeletal traction and manipulation* are among the least complicated. The former is used frequently about the knee to reduce flexion deformities. The latter is the forced stretching of a joint under general anaesthesia. Adhesions within the joint and contractures in the adjacent muscles and fascia may be loosened, although reduction of the deformity with serial plaster casts should be attempted first. Contraindications to manipulation include severe inflammation in the joint, ankylosis of the joint and marked atrophy of the bone and muscle about the joint.

Aspiration may be used to provide fluid for diagnostic purposes. In addition, pain in the markedly distended joint is decreased and irreversible stretching of the articular capsule is avoided.

Arthrotomy, the surgical opening of the joint, is sometimes of value in patients with persistent effusion. An open biopsy can be obtained for diagnostic purposes.

Synovectomy is the partial or complete removal of the synovial membrane. This procedure is frequently utilized at the time of early rheumatoid involvement of the knee or of the small joints of the hand. The articular cartilage of these joints is preserved from the damage wrought by invading pannus and by hypertrophic synovium which adheres to the cartilage and secretes lytic enzymes. At the knee, for example, the menisci and cartilage of the tibia are removed along with the

synovium and a McIntosh prosthesis is placed between femur and tibia. A new synovium grows in after surgery and it is thin, fibrous and avascular and rarely becomes inflammed.

Neurectomies are performed to relieve pain. For example, the branch of the obturator nerve supplying the anterior capsule of the hip joint can be divided.

Release of flexion contractures is frequently obtained by cutting shortened articular capsules and by 'lengthening' contracted tendons. Most often performed at the knee, surgery of this nature is indicated when flexion deformities seriously hinder function and are corrected neither by serial casts, nor by manipulation.

Osteotomy is utilized when an arthritic joint, for example a knee, is permanently ankylosed in faulty functional position. Pain is another indication as in resection of the metatarsal heads.

An *arthrodesis* is the operative fusion of a joint in the best position for function. Pain and poor functional mobility are indications.

An *arthroplasty* involves the formation of a new moveable joint when anklylosis is present or the articular surfaces are greatly distorted. An opening is made along the line of the former joint, the ends of bone are smoothed and trimmed and fascia or a prosthesis is placed between the joint surfaces.

(D) The Rheumatic Disease Unit

The concept of special centres for the treatment of rheumatic diseases has been touched upon in the guest editorial. Briefly, such a unit consists of a hospital ward area only for arthritic patients in close association with physiotherapy facilities, a Clinical Investigation Unit and laboratory space sufficient for metabolic investigations. As Ogryzlo[3] explains, "the conceptual aim has been to develop a Unit primarily for the purposes of: complete investigation of patients with rheumatic disorders; early accurate diagnosis; intensive application of accepted therapeutic procedures; and rehabilitation of those disabled patients who are capable of responding."

TREATMENT OF JUVENILE RHEUMATOID ARTHRITIS

Calabro[4] points out that patients with juvenile rheumatoid arthritis require continued reassurance and supervision and that the families must be educated concerning their care. This is especially true because of the constantly changing nature of the therapeutic programme.

The basic treatment programme is essentially as outlined for adults and includes systemic and articular rest, exercise (with children these may be done at home under parental supervision), heat application and A.S.A. Salicylates are given in six daily doses to a total of 90 mg./kg. body weight. One must be alert for the early signs of salicylate intoxication. In a patient receiving both A.S.A. and steroids, acute salicylate poisoning may occur as steroids are withdrawn.

Systemic steroids are indicated in severe systemic disease, or with chronic iridocyclitis or vasculitis. They are not required to manage pericarditis which is usually of a benign nature. In children, steroids decrease resistance to infection, retard growth and lead to cataract formation, glaucoma and vertebral collapse. On prolonged steroid therapy, children may present wtih intracranial hypertension causing headache, nausea and vomiting and papilloedema (pseudotumour cerebri). Intrasynovial steroids are used as with adults.

Gold salts may be of value in experienced hands, but the other anti-inflammatory agents ought not to be used.

Surgical treatment is comparable to that for the adult. Orthopaedic surgeons familiar with childhood problems should be consulted.

ACKNOWLEDGEMENT

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REFERENCES

1. Partridge, R. W. H. and Duthie, J. J. R.: Controlled trial of the effects of complete immobilization of the joints in rheumatoid arthritis. Ann. Rheum. Dis. 22: 91, 1963.
2. Hollander, J. L.: Arthritis and Allied Conditions. 7th Ed., 1966.
3. Ogryzlo, M. A.; Gordon, D. A. and Smythe, H. A.: The Rheumatic Disease Unit (R.D.U.) concept. Unpublished.
4. Calabro, J. J. and Marchesano, J. M.: Juvenile Rheumatoid Arthritis. N.E.J.M. 277: 746, 1967.

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Ankylosing Spondylitis

K. Cushman 6T9

INTRODUCTION

Ankylosing spondylitis (Marie-Strumpell disease) is a common cause of spinal pain and disability. A chronic progressive disease, it is characterized by an inflammatory arthritis of the sacroiliac and spinous synovial joints with adjacent soft tissue involvement. The fully developed disease exhibits variable degrees of spinal immobility as a consequence of radiologically demonstrable bony ankylosis in the affected areas. Signs of constitutional illness usually accompany the arthritic manifestations in the active stages of the disease. Peripheral joint involvement as well as specific tissue inflammations often complicate its presentation.

INCIDENCE

Ankylosing spondylitis has a predeliction for young adult males although it may occur in either sex at any age. Several reported series estimate a proportional sex incidence from 9 to 4.4 males to one female. Sharp[1] suggests that the disease affects 6 per 1000 adult males. Data compiled by West[2] indicates an incidence of .05% in the general population. However, in young adult males, hospitalization for ankylosing spondylitis constitutes approximately 20% of all patients admitted with rheumatic symptoms.

ETIOLOGY

As with other rheumatoid diseases the specific elements of causation are unknown. Both genetic factors and genito-urinary and intestinal infections have been implicated.

A genetic susceptibility indicated in several controlled studies is now generally accepted. De Blecourt[3] found that ankylosing spondylitis was 22.6 times as common in the relatives of patients with the disease as in those of normal controls. Hersh[4] in a study of 50 families concluded that inheritance of the disease is due to an autosomal dominant factor with 10% penetrance in females and 70% in males.

Genital infection has often been proposed as an exogeneous cause of ankylosing spondylitis. Older papers (Marie[5], Forestier[6]) suggest gonococcal infection as the causative factor. However, more recent series have reverted to non-specific prostato-vesiculitis. Romanus[7] found evidence of such infection in 102 of 117 males with ankylosing spondylitis. Mason[8] found evidence of prostatitis in 83% of 54 patients with ankylosing spondylitis, in 35% of 86 with rheumatoid arthritis and in 95% of 59 with Reiter's syndrome. Such observations indicate an association, but substantial causative proof is still lacking. A more nebulous relationship between ankylosing spondylitis and both ulcerative colitis and Crohn's Disease has been documented. However, the extremely variable time relationship renders the etiologic hypothesis rather dubious. No specific organism has been identified in affected tissues which could substantiate the attractive infectious theory.

In a long term study of 150 spondylitics by Rosen and Graham[9], onset of symptoms was related to infection in 15%, trauma in 23%, environmental exposure in 24% and no precipitating factor in 40% of the documented cases.

PATHOLOGY

Pathological material relative to initial development of the disease is limited. Biopsy studies by Cruickshank[10] and Rutishauser and Jacqueline[11] indicate rheumatoid alterations in the sacro-iliac, posterior intervertebral and costo-vertebral articulations. A synovitis of variable duration (months or years) instigates a cartilaginous and joint invasion by granulation tissue which eventually results in joint fibrosis. Subchondral bone undergoes a simultaneous osteoporosis and sclerosis. Obliteration of the joint space with eventual bony ankylosis is accompanied by calcification of the spinal ligaments and varying degrees of disk involvement. The nucleus pulposus, the annulus fibrosus and parts of the vertebral bodies are replaced with vascular fibrous tissue with calcification occuring in the outer fibres of the annulus fibrosus. Calcifications (syndesmophytes) adjacent to the margins of the vertebral bodies and intervertebral disks complete the picture of paravertebral ossification that accounts for the so-called "bamboo spine" appearance on X-ray.

The pathologic appearance of affected peripheral joints is indistinguishable from that of rheumatoid arthritis. Aortic valvular insufficiency has been described as a complication in 1% to 4% of patients with ankylosing spondylitis.

CLINICAL FEATURES

The majority of cases (65% to 80%), exhibit an insidious onset with complaints of lower back stiffness (especially in the morning) and pain, usually dull, aching, and of variable intensity over the lumbar and sacral regions. The pain may also present as sharp stabs over the same region occuring spontaneously, or precipitated by exercise. In some cases the pain is sciatic in nature but with no accompanying parasthesiae and often alternating from side to side. Occasionally the initial complaint is in the dorsal region, chest, neck or shoulder girdle. In 10% of cases, peripheral joint and muscle

pain is a presenting symptom. Constitutional symptoms such as fatigue, low grade fever, general aching or anorexia may accompany the primary joint manifestations and increase the difficulty in early diagnosis. Patients presenting clinically with iritis (non-granulomatous anterior uveitis), a common complication of ankylosing spondylitis, should be carefully screened for this joint disease.

Findings on physical examination relate to the severity and duration of the disease. Pain and immobility are elicited most commonly in the sacro-iliac joints (bilaterally) but may extend to any portion of the spinal column. With progression of the disease, immobility becomes the predominant feature, and tenderness and pain disappear. Straightening of the lumbar lordosis, thoracolumbar kyphosis, flattening of the anterior chest and forward cervical protrusion are features of the classic advanced spondylitic. *A most important physical sign is the degree of hip joint involvement, this joint being the key to future functional status.* Peripheral joint involvement, iritis, aortitis, myocarditis, atlanto-axial subluxation and amyloid disease may complicate the disease process in order of decreasing incidence.

The only laboratory test of value is the ESR, which is elevated in approximately 80% of cases, roughly paralleling exacerbations of the disease. A mild hypochromic anemia occurs in about 30% of cases. X-ray findings serve to confirm the diagnosis. However, lack of diagnostic X-ray findings does not preclude a clinical diagnosis of the disease due to the variability in development of detectable changes.

DIFFERENTIAL DIAGNOSIS

Early as well as atypical cases may present difficulty in diagnosis. Table 1 indicates specific factors in differentiation.

TABLE 1. DIFFERENTIAL AIDS IN DIAGNOSIS

Disease	*Features*	*Ankylosing Spondylitis*
Osteoarthritis of the spine	Sacroiliac joints normal Spinal exostoses No constitutional symptoms 5th-6th decade	Primarily sacroiliac joints Syndesmophytes Often constitutional symptoms 2nd-4th decade
Rheumatoid Arthritis	Rheumatoid serum factor Uveitis, sacroileitis uncommon Subcutaneous nodules More in females	RSF negative Common Not present Primarily males
Reiter's Syndrome	Skin lesions Achilles tendinitis Plantar fasciitis Acute, peripheral	None None None More insidious, central
Ruptured Intervertebral Disk	Local spinal involvement Neurologic changes Sciatica severe & constant	More extensive None usually Less common, often changes sides
Osteochondritis Juvenilis Dorsi	Dorsal, upper lumbar Osteophytes No constitutional illness	More lower lumbar, sacroiliac Syndesmophytes Often present
Sacroiliac Epiphysitis	Often unilateral Self-limiting No joint mottling or subchondral sclerosis	Bilateral for diagnosis Chronic progressive Both seen on X-ray

TREATMENT

The rationale of treatment is *immediate*—relief of symptoms, and *long-range*—retention of mobility and prevention of deformity.

Symptomatic relief in milder cases may be achieved by the use of salicylates alone. If a satisfactory result is not attained, phenylbutazone should be used. The initial dose is 100 mg. q.i.d. for approximately one week followed by gradual reduction to a maintenance level of 50-100 mg. daily. Drug intolerance is common (25%) and oxyphenbutazone or indomethacin may prove an effective alternative. Radiation therapy over clinically affected areas produces symptomatic relief in the majority of cases (75%). Alleviation of symptoms is usually complete and may persist for long periods. However, the threat of aplastic anemia and leukemia has eliminated its use except in cases unresponsive to more conservative measures. Steroids may be used in severe progressive disease uncontrolled by other means, but the response is unreliable and the complications severe.

The emphasis in long range treatment is on mobilization of the affected joints, coupled with postural supervision. A daily home exercise program directed towards spinal mobility, erect posture, and breathing and neck exercises ensures a good position of function when

spinal ankylosis develops. A firm bed with a flat pillow is used by the patient to avoid positions which encourage flexion deformity.

Orthopaedic splints, plaster half-shell molds and braces may be indicated when more advanced postural deformity cannot be prevented by exercise.

Surgical correction of fixed flexion deformities by osteotomy produces excellent results, but is associated with a significant surgical risk. When the hip joint is involved, arthroplasty may be indicated. However, the surgically re-constructed gap may undergo reossification.

With adequate therapy the prognosis in the disease is quite good, ultimate disability depending on the degree of hip involvement and the occurrence of complications. The critical factors in regulating the functional result of ankylosing spondylitis are early diagnosis and the co-operation of the patient in the prophylactic regimentation of his way of life.

REFERENCES

1. Shap, J. (1962): Reports on Rheumatic Diseases, No. 12. London: Empire Rheumatism Council.
2. West, H. F. (1949): The Etiology of Ankylosing Spondylitis. Ann. Rheum. Dis. 8, 143.
3. De Blécourt, J. J.; Polman, A. and De Blécourt-Meindersma, T. (1961): Hereditary Factors in Rheumatoid Arthritis and Ankylosing Spondylitis. Ann. Rheum. Dis. 20, 215.
4. Hersh, A. H.; Stecher, R. M.; Soloman, W. M.; Wolpaw, R. and Hauser, H. (1950): Heredity in Ankylosing Spondylitis; Study of 50 Families. Amer. J. Hum. Genet. 2, 391.
5. Marie, P. (1898): Rev. Méd. (Paris), 18, 285.
6. Forestier, J. (1939): Radiology, 33, 389.
7. Romanus, R. (1953): Pelvo-Spondylitis Ossificans in the Male (Ankylosing Spondylitis) and Genito-Urinary Infection. Study of 117 Male Patients. Acta Med. Scand. 145. Suppl. 280.
8. Mason, R. M.; Murray, R. S.; Oates, J. K. and Young, A. C. (1958): Prostatitis and Ankylosing Spondylitis. Brit. Med. J. 1, 748.
9. Rosen, P. S.; Graham, D. C. (1962): Ankylosing Spondylitis; A Clinical Review of 128 Cases. Archives Inter-Amer. Rheum. 5, 158.
10. Cruickshank, B. (1956): Lesions of Cartilaginous Joints in Ankylosing Spondylitis. J. Path. Bact. 71, 73.
11. Rutishauser, E. and Jacqueline, F. (1955): Documenta Geigy, No. 16.

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The Kidney And The Collagen Diseases

P. F. Halloran 6T8

The so-called collagen diseases have in common many features suggesting a disordered immune response. Whether the pathological immune reactions noted in some of these diseases are primary or secondary, significant or insignificant in the etiology and pathogenesis, has not been established. Nevertheless, there is a strong possibility that immune mechanisms may play a role in the tissue damage seen in some of these diseases.

The purpose of this article is to discuss the known experimental "immune" mechanisms for renal damage, and to discuss against this background the renal manifestations of the collagen diseases.

EXPERIMENTAL MODELS FOR RENAL DAMAGE BY IMMUNE MECHANISMS

The models we shall discuss will be: Masugi nephrotoxic serum nephritis; experimental serum sickness nephritis; the NZB mouse nephritis; the renal homograft rejection reaction.

(1) Masugi nephrotoxic serum nephritis

In 1933, Masugi obtained antiserum against rat kidney in ducks or rabbits by withdrawing from the injected animal serum rich in anti-rat kidney antibodies. Subsequently, injection of the anti-rat kidney serum into rats produced nephritis. Earlier, investigators had produced acute nephritis, but Masugi was the first to produce chronic nephritis, characterized by proliferative changes in the glomerular tuft with epithelial crescents and glomerular obliteration.

The reaction is mediated by the fixation of rabbit γ-globulin to the glomerular basement membrane in the presence of complement. But the host rat produces antibodies to the rabbit globulin, and these combine with their antigen in the glomerular basement membrane as well. Which of these two immune reactions is of greater significance in the pathogenesis of Masugi nephritis has not been clearly established, and may vary with the species involved.

Investigators attempting to implicate "auto-immune" phenomena in acute glomerulonephritis have demonstrated anti-human kidney antibody in 71% of cases studied, and in 89% of cases of membranous glomerulonephritis. This probably reflects tissue damage, and not a primary event; anti-heart antibodies, it will be recalled, can be demonstrated after myocardial infarction.

The safest interpretation of Masugi nephritis is simply that localization of antibody and its antigen in the GBM, along with activation of complement, can mediate acute and chronic glomerulonephritis morphologically similar to human diseases. This would then suggest a common pathway between Masugi nephrotoxic serum nephritis and serum sickness nephritis which will be discussed below.

(2) Serum sickness nephritis

Patients receiving prophyllactic horse serum injections frequently develop at four to ten days after injection a disease characterized by urticaria, fever, lymphadenopathy, edema, headache, nausea, and symptoms of mononeuritis. The urine may contain protein, erythrocytes, and casts. The reaction is rarely fatal, subsiding usually within three weeks. Pathologically, the characteristic lesion is an angiitis "indistinguishable from . . . that of polyarteritis nodosa" with frequent occurrence of acute nephritis.

In the experimental animal, the pathology shows acute proliferative glomerulonephritis, arteritis, endocarditis, and myocarditis. The lesions and symptoms appear during the period when soluble antigen-antibody complexes are circulating with an excess of antigen, and disappear with the appearance of excess antibody as the immune response progresses. To elaborate upon this, let us consider the stages in the response to circulating foreign protein (see Fig. 1.). After an initial slight, sharp drop, the level of circulating antigen begins to drop slowly in subsequent days in a predictable, exponential fashion as the animal destroys it by "non-immune" mechanisms (see Fig. 1.). In a tolerant animal, the curve continues to fall in this exponential fashion until the level of antigen becomes negligible. However, most animals begin about day four to six to produce specific antibody, which in the presence of excess antigen, forms complexes of Ag_2Ab. As more antibody is produced, progressively more antibody combines with each unit of antigen until excess antibody disappears, excess antigen disappears, and the complexes are taken up by the reticuloendothelial system. This reaction can be characterized by the following:

$$\underset{\text{(excess)}}{Ag} \rightleftharpoons Ag_2Ab \rightleftharpoons Ag_3Ab_2 \rightleftharpoons AgAb \rightleftharpoons Ag_2Ab_3 \rightleftharpoons AgAb_2 \rightleftharpoons \underset{\text{(excess)}}{Ab}$$

The reaction proceeds to the left as the animal produces antibody at a faster and faster rate, and the tissue toxicity of the complexes increases as the molecular weight increases. However, uptake by the reticuloendothelial system clears the larger complexes from the plasma. Hence, toxic complexes such as Ag_3Ab_2 are present in the circulation only during a brief period as antibody levels are rising, until the antibody excess state appears. As illustrated in Fig. 1., this critical time coincides with the appearance of serum sickness lesions,

particularly nephritis. After the critical period is over, high levels of specific antibody exist, and any subsequent antigen injections produce no lesions, since the above reaction proceeds to the left so quickly that Ag_3Ab_2 complexes are not allowed to exist in the circulation. Thus the nephritis and other lesions heal.

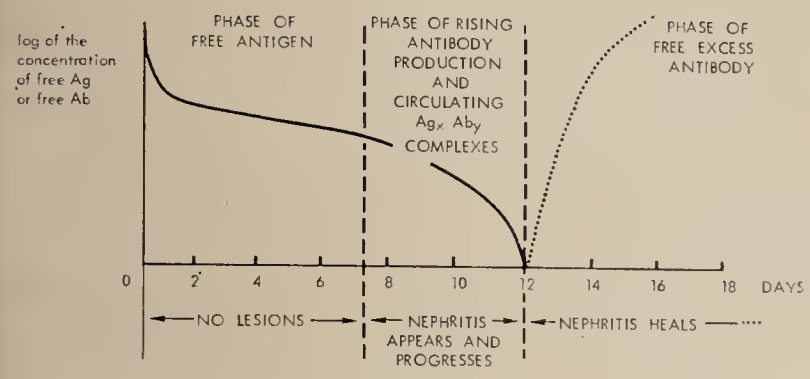

FIG. 1.

The above sequence occurs with normal antibody producers, in the face of chronic daily antigen injections. However, in animals which produce no antibody to the antigen, no serum sickness lesions will develop. In animals who never produce enough antibody to shift the reaction to the left, but who always continue to produce low levels of antibody, the lesions will refuse to heal, and progressive nephritis is seen. Finally, there is one group of animals which produces antibody well at first, then poorly at a later date. These animals have the toxic complexes briefly at first, then not at all for an indefinite period, only to have the toxic circulating Ag-Ab complexes return at a late date as antibody production falls to low levels. Consequently their course is an acute nephritis which heals, and is followed by chronic nephritis.

Thus a given antigenic stimulus to a population of animals will produce no lesions, acute lesions, acute progressive lesions, or chronic lesions, depending on the type of antibody response.

(3) The NZB mouse nephritis

Intraperitoneal injection of homologous kidney tissue with Freund's adjuvant into rabbits has succeeded in producing a nephrotic syndrome with glomerular and tubular lesions. This "auto-immune" reactivity against the rabbit's own kidney could be passively transferred by lymphocytes but not by sera, and circulating antibody was not demonstrable.

The relevancy of auto-immune nephritis to human renal disease has been enhanced by the discovery of the NZB (New Zealand Black) strain of mice, who develop spontaneously a wide variety of pathological immune reactions. In the early months of life, germinal centres of hyperplasia occur in the thymus; Coombs$^+$-positive hemolytic anemia develops; anti-nuclear factors with a positive LE cell preparation appear; and a severe renal disease develops, characterized by focal (wire-loop) and diffuse membranous changes, progressive narrowing of capillaries, and ultimate hyalinization of glomeruli. Diseased glomeruli can be shown to contain γ-globulin with the characteristics of auto-antibody against glomerular antigens. The pathological similarity to lupus nephritis is striking.

(4) The renal homograft rejection reaction

This process has been reviewed in a recent edition of this journal, and no attempt shall be made to repeat that discussion. However, one aspect of the pathology of this reaction is relevant to the present discussion, and bears repeating. In rare instances the rejection reaction has been associated with an acute vasculitis in the transplanted kidney in recipients previously sensitized by platelet transfusions or tissue from the same donor. In this, one sees fibrinoid necrosis of small arteries, arterioles, and glomerular tufts, with extensive infarction and acute deterioration of renal function. Apparently, this reaction is mediated by circulating antibody, and is unaffected by immunosuppressives. The similarity of this reaction to the lesions of hypersensitivity angiitis or polyarteritis nodosa may be significant.

Summary of the immune models

(a) The localization of antibody, antigen, and complement within the glomerular basement membrane can cause proliferative or membranous changes in the glomerulus which may progress to chronic renal failure.

(b) Antibody directed against tissue antigens in the kidney can cause acute vascultis with infarction. However, vasculitis can be mediated by circulating immune complexes which do not specifically involve tissue antigens, as in serum sickness.

RENAL INVOLVEMENT IN THE COLLAGEN DISEASES

The kidney is involved to a serious degree in many of the collagen disorders, and is the most common cause of death in several—chiefly DLE, polyarteritis nodosa, thrombotic thrombocytopenic purpura, Wegener's granulomatosis, and Goodpasture's syndrome. (see Table 1.) Of these, lupus nephritis is the most common, the most thoroughly investigated, and the one in which the most significant progress in treatment has been made. We shall devote much of our discussion, therefore, to lupus nephritis.

(1) Lupus nephritis

Systemic lupus erythematosus is characterized by a variety of abnormal reactions: the appearance of antinuclear antibodies, which are responsible for the LE cell phenomenon *in vitro* and the hematoxylin body *in vivo*; Coombs$^+$ hemolytic anemia and "auto-immune" thrombocytopenia and granulocytopenia: hyperglobulinemia involving 7s and 19s immunoglobulins: antibodies to

TABLE 1. INCIDENCE OF RENAL INVOLVEMENT IN COLLAGEN DISEASE

Disease	*Clinical* %	*Pathological* %	*Renal Death* %	*Duration (Years) of Illness*
Systemic Lupus Erythematosis (SLE)	50 - 80	80 - 100	40 - 50	1 - 10
Polyarteritis Nodosa (PAN)				
Classical PAN	70 - 100	70 - 100	50 - 60	1 - 4
Hypersensitivity Angiitis	100	100	90	< 1
Progressive Systemic Sclerosis (Scleroderma) (PSS)	15	40 - 50	5 - 15	1 - 10
Rheumatoid Arthritis (RA)	10 - 30	10 - 20	5	3 - 20
Dermatomyositis	5	1	0	
Anaphylactoid Purpura (AP)	20 - 60	20 - 60	2 - 5	2 - 10
Wegener's Granulomatosis	90 - 100	90 - 100	80 - 90	< 1
Goodpasture's Syndrome	100	100	90	< 1
Thrombotic Thrombocytopenic Purpura	95	90 - 100	50 - 70	< 1

thyroglobulin and thyroid tissue; depressed levels of complement prior to and during exacerbations; and many other suggestions of disordered immune reactions.

Persons with hypogammaglobulinemia appear to have an increased frequency of lupus and rheumatoid arthritis, and lupus-like syndromes have been reported following various drugs, notably hydralazine.

The presence of renal disease in SLE, particularly at the onset of symptoms, is perhaps "the most ominous of the many manifestations of the disease." It is particularly serious in those under 30 years of age and in males. It may be present on renal biopsy without clinical evidence, but usually is clinically apparent.

The clinical manifestations of SLE nephritis vary in severity from slight abnormalities in the urinary sediment to full-blown nephrotic syndrome or uremia. Hypertension is frequently present in nephritis; hypertension rarely occurs in the absence of nephritis, but nephritis is present without hypertension not infrequently. The urine may show protein in the absence of abnormal sediment, in which case biopsy will often prove abnormal. Typically, the urine in lupus nephritis has a "telescoped sediment", with simultaneous evidence of nephritis (erythrocytes, erythrocyte casts, and leucocytes), nephrosis (fatty, hyaline, granular, and waxy casts, and oval fat bodies), and chronic renal failure (broad casts). Renal function, however, may be normal because of the local, focal nature of the disease, or may be abnormal with more diffuse and generalized glomerular damage (depression of clearances and PSP excretion). A full-blown nephrotic syndrome occurs in 30% of patients, but may be unusual in that cholesterol levels may be normal. Renal failure with uremia is a common cause of death, after an average course of one to two years of active renal disease.

The pathology of the renal lesion in SLE has been extensively studied by renal biopsy. The glomerular lesion may follow one of three patterns:

(a) *Active lupus glomerulonephritis*

This is the most serious renal lesion, and is the cause of the typical clinical manifestations of lupus nephritis. The lesion tends to progress from a local, focal distribution to a generalized, diffuse involvement. Histologically, the lesion consists of focal proliferation of endothelial and mesangial cells, with irregular thickening of the GBM and epithelial crescent formation. However, several features distinguish lupus glomerulonephritis: "wire-loop" lesions, karyorrhexis, and local necrosis in the glomerular tuft, hematoxphil bodies, and "hyaline thrombi" in capillary loops.

The electron microscope has revealed that the wire-loop is produced by accumulation of electron-dense, "osmophilic" material between the endothelium and the basement membrane. This material is also seen focally in endothelial and mesangial cell cytoplasm, and has been postulated to be either fibrinogen derivatives or immune complexes. In those with active glomerular disease, the GBM stains heavily for γ-globulin, fibrinogen derivatives, and complement. It has been postulated that an immune reaction activates the clotting mechanism locally, as has been shown to occur *in vitro*.[12]

Abnormalities of the remainder of the parenchyma are usually present, such as interstitial infiltration by lymphocytes and plasma cells, tubular abnormalities, and less commonly, angiitis.

Renal biopsy studies have revealed that the active lupus glomerulonephritis lesion progresses to a diffuse, generalized disease with epithelial crescent formation, indistinguishable histologically from "subacute" and chronic glomerulonephritis. Uremia and death usually follow.

(b) *Lupus glomerulitis*

Here, focal proliferative changes are noted at the periphery of the glomerular tufts, and the basement mem-

brane may be thickened. However, "wire-loop" lesions, focal necrosis, karyorrhexis, and hematoxyphil bodies are absent, and there are no extra-glomerular changes. Biopsy studies have demonstrated that this lesion does not progress to lupus glomerulonephritis or renal failure.

(c) *Membranous lupus glomerulonephritis*

The lesion is histologically identical to membranous glomerulonephritis of unknown origin seen in individuals without SLE. Like the latter, ultrastructural studies reveal GBM thickening, with electron-dense deposits between the epithelial foot processes (which are fused), and the GBM. No subendothelial deposits are demonstrable. Prognosis, like that of lupus glomerulitis, is relatively good, but proteinuria may be considerable.

The treatment of lupus nephritis must not be divorced from the treatment of SLE itself. (Indeed, no special treatment is required for individuals with membranous lupus GN or lupus glomerulitis.) When lupus GN is absent, prednisone is usually employed in doses adequate to suppress symptoms, with maintenance dosage of 10-20 mgm/day. It is seldom necessary to make the patient "Cushingoid". However, in patients with lupus GN, high dosages of steroids employed over long periods of time are required to effect a significant improvement in prognosis. In Pollak's classic study, dosages of 40-60 mgm prednisone per day were employed with significant improvement in survival over a group treated with lower dosages. This therapy was maintained for six months, after which time dosages were reduced to less than 40 mgm/day. Current treatment is usually less dogmatic than this, employing high dosage only as long as is necessary "to suppress all manifestations" of acute renal disease, then switching to the minimal dosage required to maintain remission. A new dosage schedule for glucocorticoids, administering the same total quantity as a single dose every two days instead of daily in divided doses, may reduce the incidence of side effects, and is currently under appraisal.

Favourable reports on the use of nitrogen mustard, 6-mercaptopurine, and azathioprine have appeared.

The effects of steroid and immunosuppressive therapy are similar, causing complete regression of many of the less severe changes of acute nephritis. However, necrotizing changes, if prominent, tend to heal by partial fibrosis of the glomerular tuft, and interstitial and glomerular fibrosis are common in renal biopsies of persons with steroid-induced remissions.

The prognosis in those with active lupus GN is not good. Pollak found that his group with low dosage steroid treatment averaged 14 months survival, while on high dosages averaged 26 months. Azotemia or nephrotic syndrome apparently reduce the prognosis because they reduce the probability of a remission, but if remission can be induced, prolonged survivals can be obtained.

(2) Polyarteritis nodosa

This term should be recognized as encompassing two clinical entities: classical PAN, and hypersensitivity angiitis. The features of these illnesses are outlined in Table 2. In addition, an allergic granulomatous variant is also recognized, being similar in most of its features to hypersensitivity angiitis, with the additional features of a history of allergic respiratory symptoms and pathological findings of necrotizing granulomas. Wegener's granulomatosis is related to this entity, but differs in that midline granuloma is added and the eosinophilia is usually absent.

Table 2.

Classical Polyarteritis Nodosa	*Hypersensitivity Angiitis*
No definite history of antigen	Definite history of exposure to antigen
Eosinophilia absent to moderate	Eosinophilia marked
Lungs usually spared	Lungs usually involved
Hypertension common	Hypertension absent
Lesions involve medium-sized and small muscular arteries	Lesions involve arterioles venules, capillaries, and some small muscular arteries
Lesions different ages	Lesions same age
Chronic relapsing course	Relentless progression

Polyarteritis may be found in association with SLE, rheumatoid arthritis, scleroderma, dermatomyositis, or thrombotic thrombocytopenic purpura. Hypersensitivity angiitis has followed exposure to drugs, (sulfonamides, penicillin, thioureas, iodides, Dilantin) horse serum, and other antigenic stimuli, particular those producing respiratory allergy or otitis media. A disease very similar to PAN occurs "spontaneously" in Aleutian minks and in other animals, and the question of an infectious etiology has been raised here.

The clinical manifestations of renal involvement with PAN usually include hypertension (less common in hypersensitivity angiitis), proteinuria, hematuria, "telescoped" urinary sediment as in SLE (see above), azotemia, and renal failure. Hypertension may be "malignant". Pain in the lumbar areas is not uncommon.

Pathologically, the classical form tends to affect arcuate-sized arteries most severely, with frequent aneurysm and infarct formation, while glomerular involvement tends to be mild, with mild proliferative and focal necrotizing changes. The acute lesion may be seen side by side with the healing lesion. Hypersensitivity angiitis tends to cause complete destruction of the entire vessel wall, with extensive proliferation and necrotizing GN which is diffuse and often generalized in distribution and is associated with epithelial crescent formation. Some glomeruli may be spared, however. As can be imagined, the pathological pictures tend to overlap in large vessel and glomerular involvement.

Treatment with steroids, particularly in the classical idiopathic form of PAN, may be associated with prolongation of life in some cases. The arterial lesions tend to heal by fibrosis with severe intimal narrowing, thus aggravating hypertension and ischemic symptoms.

The prognosis in the face of renal involvement is usually poor, and renal failure is a frequent terminal event, particularly in the hypersensitivity angiitis variant.

(3) Scleroderma

Renal involvement in scleroderma is not common, occurring in severe form in only 5% of cases. When significant, it is usually associated with malignant hypertension and hypertensive encephalopathy, and death is imminent.

Two clinical patterns of scleroderma are recognized; one, an acute form, with early visceral involvement and rapidly progressing renal disease; the other chronic, with late visceral involvement, but with renal complications resulting in short survival.

Two types of renal vascular lesion are seen: a mucoid type of intimal thickening, rich in mucopolysaccharides, seen in older individuals with acute scleroderma; and an elastic hyperplasia type of intimal thickening, characterized by many concentric laminae of elastic tissue, seen in younger patients with more chronic disease. Both types occur most frequently in interlobular-sized arteries; both may occur in the absence of hypertension, but the elastic lesion is much more commonly present without hypertension than the mucoid. Malignant hypertension may add fibrinoid changes to the lesions outlined above, particularly in the afferent arterioles and glomerulus. Renal function studies indicate that renal plasma flow is considerably reduced by the arterial narrowing, but that glomerular filtration is maintained by efferent arteriolar constriction. However, the relative ischemia of the kidney is probably etiologically significant in the hypertension, as witnessed by the hyperplasia of the juxta-glomerular apparatus which has been noticed in this disease.

Occasional wire loops or proliferative glomerular changes may occur, but glomerular damage is rarely prominent; hence proteinuria is seldom severe.

Corticosteroids are ineffective in scleroderma, and may exaggerate hypertension.

(4) Rheumatoid arthritis (RA)

Proteinuria is fairly common in RA, but nephrosis, azotemia, and renal failure are not. When significant renal disease is present, it is usually amyloidosis, but may rarely represent coexistence of SLE or PAN, both of which may occur in RA.

Pathologically, a proliferative glomerulitis has been described in RA, but it is invariably mild and insignificant clinically. However, amyloidosis is a significant clinical problem. It is usually of the "secondary" type in its staining and distribution. It occurs in direct relationship to the duration and severity of the disease, and may progress from mild proteinuria to chronic renal failure with or without an intervening nephrotic syndrome. Hypertension is said to develop relatively late in renal involvement with amyloidosis.

The nature of amyloid is currently in doubt. It appears to be at least in part a fibrillary protein which binds either γ-globulin or fibrinogen derivatives nonspecifically. In the glomerulus, it is located inside the basement membrane, but when extensive, may be present outside the GBM as well. It eventually obliterates the glomerulus.

No treatment for amyloidosis is known.

(5) Renal involvement in other diseases related to the collagen disorders

Table 1. provides an indication of the frequency and severity of renal disease in these disorders. Space limitations prevent discussion of these disorders, except to indicate that renal involvement in general is an ominous prognostic sign in this group.

SUMMARY

Renal involvement is frequent and severe in the so-called collagen diseases and their relatives. The widespread manifestations of these disorders prevent the consideration of affected patients for chronic hemodialysis or renal homotransplantation. Suppression of immune responsiveness by glucocorticoids and immunosuppressives at present appears to be the only available treatment. More successful treatment awaits further understanding of the pathogenesis of glomerular disease and of the collagen disorders, in general.

ACKNOWLEDGEMENT

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BIBLIOGRAPHY

SPACE CONSIDERATIONS HAVE NECESSITATED DELETION OF REFERENCES; THESE ARE AVAILABLE ON REQUEST FROM THE AUTHOR.

Student Research

Autoimmunity And Degenerative Arthritis In Rabbits

An autoimmune response is produced by the formation of antibodies to antigens arising from an individual's own tissues. There are certain tissues in our body which remain autonomous from the general systemic circulation, and therefore do not take part in the general body physiology. Such so-called avascular tissues are: C.S.F., aqueous and vitreous humor, thyroglobulin, the lens of the eye, nucleus pulposus, tendon sheaths, and others. In this particular experiment the antigenic component of the autoimmune reaction is the articular cartilage of the knee and ankle joints of the rabbit. This material is justifiably employed as an auto-antigen since it is totally avascular, and is therefore not recognised as being part of 'self'. Articular cartilage then, may be considered as analogous to the other avascular tissues enumerated previously.

As for the site of antibody production, recent evidence points to the regional lymph nodes as being the areas first involved. Antibody produced here is hypothesized as being 'cell-bound', and in this state the antibody is carried to the site of antigen deposition by efferent lymphatic vessels. It is at this site that the antigen-antibody reaction occurs, with subsequent inflammatory and degenerative changes.

With these points in mind the experiment was set up with the purpose of inducing the production of autoimmune antibodies in primary regional lymph nodes (in this case the popliteal nodes on the medial aspect of the knee joint), in response to the vascularization of the animal's own articular cartilage following deposition in various sites in either hind limb. The rabbits were then autopsied at regularly spaced intervals, and the regional popliteal lymph nodes were excised, sectioned, and stained with Methyl Green Pyronin (a non-specific stain for RNA) for the presence of 'cell-bound' antibody.

PRIOR WORK

It has been shown that homografts, presumably via an Ag-Ab reaction, provoke the presence of large pyronin +ve mononuclear cells in local lymph nodes, this being an early limited response suggestive of a regional immunological transaction which precedes a more readily demonstrable generalized state of hypersensitivity. These findings would seem to corroborate our work to the extent that the transplantation of rabbits' articular cartilage is representative of a homograft.

As regards this particular project, prior work consisted of using articular cartilage removed from the knee joint, and placed subcutaneously in the ear of a rabbit, producing, it was found, a uniform lymphoid response (i.e. a pyronin +ve reaction), which was most marked at the primary regional lymph node. It should be noted however, that this response was also noted to a lesser degree in the adjacent secondary nodes. Controls, using muscle implanted subcutaneously, yielded no reaction in the nodes—(Muscle, not being an avascular tissue, is therefore recognized as part of 'self').

The other phases of the experiment were undertaken. The first, Part A, consisted of performing surgical trauma to both knees of a rabbit, along with the unilateral removal of the popliteal (regional) lymph node. The gross pathology with respect to the joints of animals sacrificed at two week intervals from one to six months, was more marked in the knee joints of animals which retained the popliteal lymph node. This pathology consisted of:

1. Marked synovial thickening.

2. Enlargement of the surgically denuded area, and fissuring of the adjacent cartilaginous surfaces.

3. In the knee with prophylactic lymph node excision, there was more rapid healing with reduction in the amount of progressive degeneration.

4. The *in situ* node showed hypertrophy plus an increased pyronin response, suggestive of an immunological reaction.

5. No distant nodes were affected.

Part B of the project involved surgical trauma to one knee and a simple arthrotomy to the other, both regional nodes being left intact. This surgical trauma consisted of opening the knee joint, exposing the distal end of the femur, and scraping the articular cartilage off the medial condyle of the femur. The cartilage was then minced and implanted into the knee joint of the ipsilateral side. The knee was then sutured with chromic catgut and silk. As mentioned, a simple arthrotomy was carried out on the contralateral knee joint as a control.

The histological picture at 4 to 8 weeks showed 50 to 100% hypertrophy of the regional node, with increased pyronin only on the side with vascularizing cartilage. This is very suggestive of an auto-immune response in the regional node.

Three new phases, Parts C, D and E of the experiment are now in progress, involving three variants of the operative procedure previously described. Part C consists of opening the knee joint of one side, scraping

and mincing the cartilage off the medial femoral condyle, followed by implantation of the cartilage subcutaneously beside the knee (or ankle) joint of the opposite limb.

Part D involves opening of the ankle joint of one limb, scraping the lower end of the tibia of its articular cartilage, and implantation of the cartilage in that same ankle joint. A simple arthrotomy is performed as a control on the ankle joint of the opposite limb. Both popliteal nodes remain *in situ*.

The operative technique in Part E is as follows: scrape both tibias at their distal articulations; implant the cartilage obtained into both ankle joints; leave the right popliteal node intact, and remove the left node.

The relevancy of these new phases of the project is apparent when one considers the lymph drainage system of the rabbit's hind limb. It has been shown by a series of vital staining procedures using sky-blue dye, that the knee joint does not drain directly to the popliteal node, but rather, drains to the femoral vessels, and then on to the peri-aortic nodes. It must, however, be noted that the extensor hallucis longus is surrounded by a synovial tube joining the knee to the region of the ankle. Therefore, antigen production in the knee joint is conveyed through the ankle to the popliteal node.

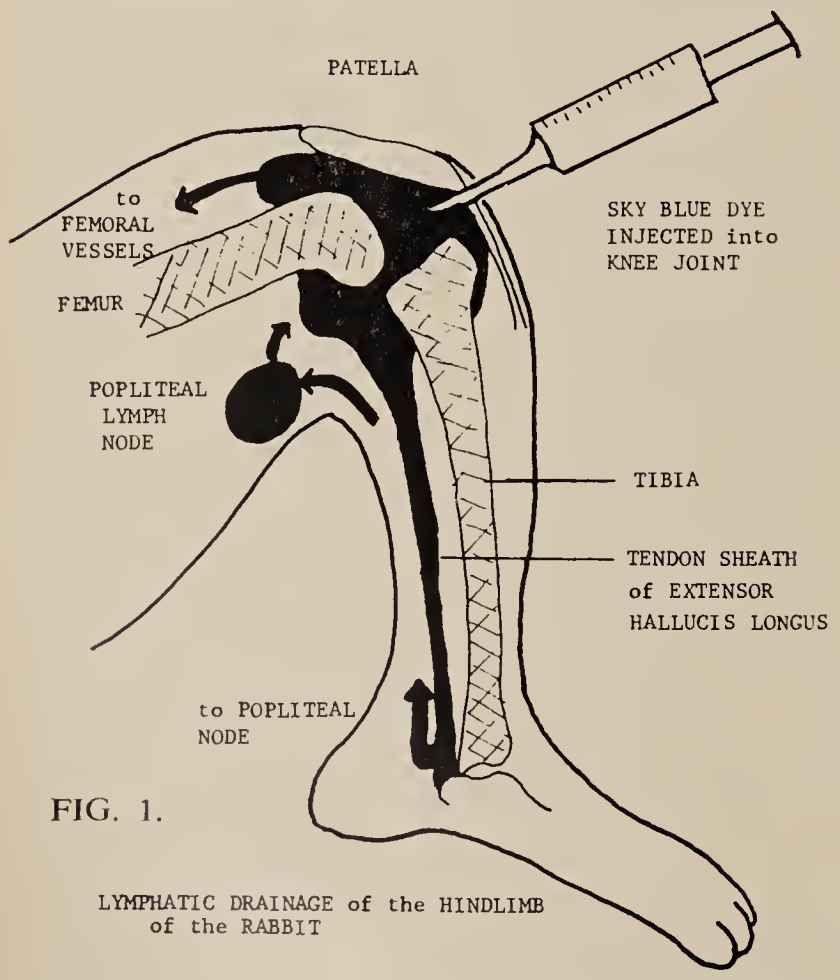

FIG. 1.

LYMPHATIC DRAINAGE of the HINDLIMB of the RABBIT

These facts have important implications regarding the relative degree of severity of the autoimmune reaction both at the knee and ankle joints, for since the ankle joint drains directly to the popliteal node, foreign material (i.e. articular cartilage) implanted either subcutaneously beside or directly into the ankle joint, should theoretically cause a more severe autoimmune response in the node than cartilage deposited in comparable sites in and around the knee joint.

Thus, in Part C, cartilage implanted subcutaneously beside the ankle joint should theoretically evoke a greater reaction in the regional node, than cartilage implanted subcutaneously at the knee joint. Similarly, in Part D, cartilage deposited directly into the ankle should cause a more severe autoimmune response in the popliteal node than in previous experiments described which involved the knee joint—direct cartilage implantation technique. It should be noted that in Parts C and D, all the regional lymph nodes are left *in situ*. The findings to date indicate that our prior assumptions were correct, that is, surgical involvement at the ankle joint induces a more severe autoimmune response in the popliteal node, as compared with surgical trauma about the knee joint.

Part E, as was noted, involves surgical trauma to both ankles, with the subsequent excision of the left regional node. If the theory holds that the regional node is indeed the manufacturer of antibody involved in the Ag-Ab reaction, then a greater degree of destructive change in the limb which retained the popliteal node, should be found. (i.e. greater destructive changes in the ankle joint of that limb, as compared with the opposite limb which had the regional node excised at the time of operation.) Early findings in this area of the work seem to confirm our hypothesis that with the node *in situ*, the autoimmune response in the joint is greater.

SUMMARY

In recent years, with the increasing importance being placed on autoimmune mechanisms as a causative factor in many diseases, it has been postulated that a similar mechanism may be in operation in degenerative arthritis. With this postulate in mind, a series of experiments has been undertaken with the combined purposes of:

1. Confirming or disproving the hypothesis of autoimmune involvement in degenerative arthritis.
2. Determining the site of antibody formation leading to an Ag-Ab reaction.
3. Investigating the nature of the lymphoid response to articular cartilage degeneration, and
4. Investigating grossly and microscopically the nature of the degenerative changes which follow in the path of the autoimmune response.

This work may be of significant aid in the understanding of degenerative articular conditions, and, going one step further, may have possible applications in the field of rheumatoid disease, which is presently hypothesized as being within the realm of autoimmune diseases.

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The Heart

INTRODUCTION

The radiologic examination of the heart and great vessels often affords the physician invaluable information concerning the type and severity of heart disease present. Therefore, because of the great importance of heart disease, this article will be *specifically* devoted to the radiologic examination of the heart in cardiac disease.

Routinely the heart is examined on the standard 6-foot P.A. film (which enlarges the heart by projection less than 5%) and on the left lateral projection. More detailed cardiac evaluations require oblique projections and often the use of angiocardiography, which will be discussed in a future issue dealing with special procedures. In the oblique projections, the right anterior oblique is made with the right anterior axillary line against the casette, and the left anterior oblique is made with the left anterior axillary line against the casette. In this way different views of the cardiac silhouette can be visualized to determine more definitely which, if any, of the heart chambers is involved.

NORMAL CARDIAC SIZE AND CONTOUR

The simplest method of measuring the heart is to determine its relationship to the width of the chest at its widest point near the level of the diaphragm. This is called the *cardiothoracic ratio* and is carried out on the PA 6-foot chest film only. Measurement is taken between 2 vertical lines drawn tangential to the most prominent point on the right and left cardiac profiles. The prominence of the bulge on the right is usually a little higher than the apex on the left profile. In adults, the width of the heart should be *less than half the widest thoracic diameter,* measured from inside the rib cage. The normal PA heart profile can best be studied by inspecting the normal anatomical landmarks in Figure 1A.

NORMAL VARIATIONS IN THE HEART

The heart, like other anatomic structures, may vary within fairly wide limits. Apparent cardiac enlargements may be caused by one or several of the following factors:

1. Phase of Respiration: Inspiration views tend to lower the diaphragms and elongate the heart. Expiration views show a high diaphragm and a flattened-out heart, bringing the apex closer to the lateral chest wall.

2. Any condition producing abdominal distension, such as ascites, or late pregnancy, also cause high diaphragms.

3. Portable chest films are made AP and because the heart is further away from the film, there is an appreciable enlargement of the heart shadow.

4. Any degree of rotation off the sagittal plane (excluding oblique views) may produce an appearance of widening of the heart and mediastinal shadows.

5. Any deformity of the thoracic cage, for example severe scoliosis, will render accurate cardiac measurement almost impossible.

6. The heart in females is approximately 5% smaller than in males, in proportion to body size.

LEFT VENTRICLE

The main portion of the left ventricle faces laterally and posteriorly, only a small portion faces anteriorly and this helps to make up the left heart border on the PA film. The radiologic signs of left ventricular enlargement are:

1. Outward and downward displacement of the left lateral contour on the PA film.

2. Increase in the convexity of the left lateral contour in the PA view.

3. Rounding of the upper portion of the left ventricle in the left anterior oblique view.

Extensive left ventricular enlargement occurs in aortic insufficiency and in hypertension. Lesser grades of left ventricular enlargement occur in aortic stenosis, coarctation of the aorta, mitral insufficiency, arteriovenous shunts and acute rheumatic fever with pancarditis. The left ventricle may not be enlarged in aortic valvular disease if there is concomitant mitral stenosis severe enough to decrease the diastolic filling of this chamber. In addition, a left ventricle that has previously been enlarged may subsequently atrophy if a complication such as pulmonary T.B. or some other debilitating disease supervenes. A problem often arises when one tries to distinguish between cardiac hypertrophy and cardiac dilatation. Suffice it here to say that a hypertrophied heart tends to have a sharply outlined, firmly rounded contour for its enlarged shadow. When this hypertrophied heart goes into failure, it decompensates and dilates, it will lose to some extent its well rounded contours and gradually increase in width. The additional indications of the failing heart found in the lungs have been described in the previous issue.

LEFT ATRIUM

The left auricle lies in front of the vertebral column, esophagus and descending aorta. It extends almost equally to the right and to the left of the midline and is posterior and somewhat superior to the left ventricle. The tip of the left auricular appendage helps to form a part of the left cardiac contour in the PA view. The sequence of left auricular enlargement is posteriorly to the

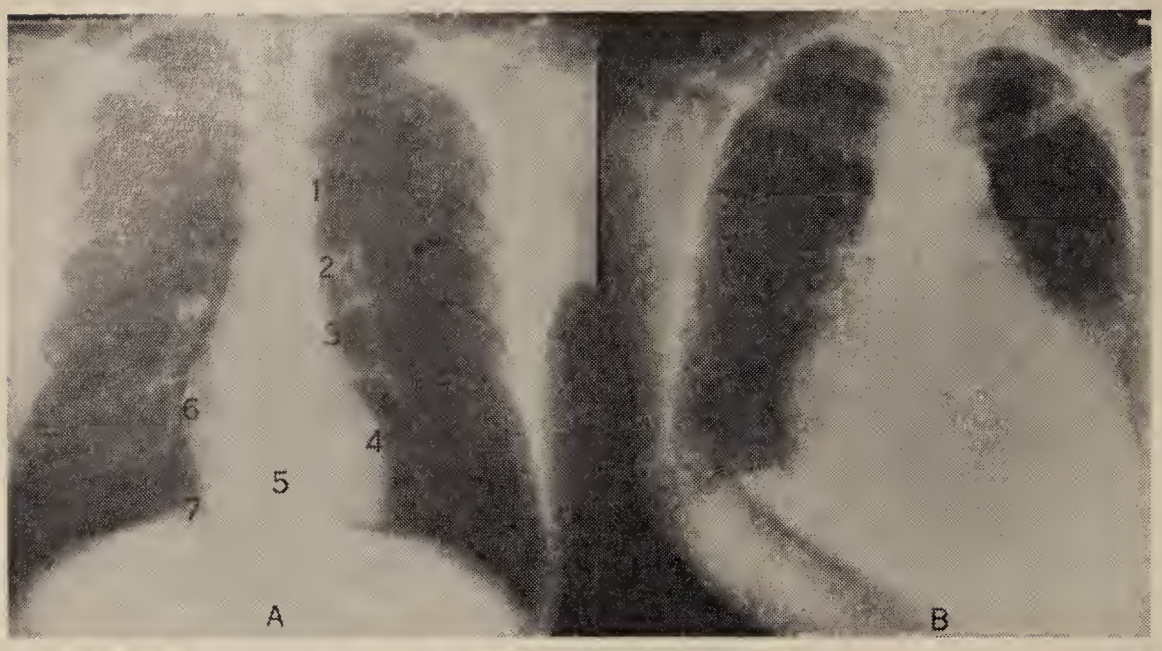

FIG. 1.

(A) Normal heart, P-A view.
1 - Aortic arch; 2 - Pulmonary trunk; 3 - Left atrial appendage area; 4 - Left heart border or left ventricle; 5 - Area of right ventricle; 6 - Right heart border or right atrium; 7 - Inferior vena cava.

(B) Unknown 1 — Markedly enlarged heart — see article.

FIG. 2.

(A) Normal heart, left lateral view.
1 - Posterior (retro) cardiac space; 2 - Anterior cardiac space; 3 - Area of left atrium; 4 - Area of right ventricle.

(B) Unknown 2 — see article.

right, superiorly and finally to the left. Enlargement anteriorly is limited because of the resistance offered by the mitral valve and left ventricle. The significant radiologic features of left atrial enlargement are:

1. 'Straightening' of the left heart border (PA view) caused by the enlarging left artial appendage filling-in the small concavity which is normally seen as part of the left cardiac contour.

2. Elevation of the left main bronchus and splaying of the carina from upward left atrial enlargement (PA view).

3. When the left atrium is enlarged the barium-filled esophagus is indented and displaced to the right (PA view), and is rounded posteriorly (lateral view).

4. The left atrial shadow may be visualized within the cardiac shadow in the PA view as a central area of increased density which may approach and form part of the right cardiac contour. Such a density, within what was the right atrial shadow is referred to as a "double contour".

5. Encroachment on the retrocardiac space (i.e. the space on the lateral film between the posterior aspect of the heart, and the spine). The extent of horizontal enlargement of the left atrium can be inferred from the degree of overlap of the spine and the degree of posterior compression or displacement of the barium filled esophagus in the lateral view.

The two most frequent causes for left atrial enlargement are rheumatic mitral disease (both stenosis and insufficiency) and total left ventricular failure.

RIGHT VENTRICLE

The right ventricle is the most anterior of the heart chambers. To its left and posteriorly is the left ventricle. To its right is the right atrium. It is therefore not represented radiologically as part of the left or right heart borders. The main radiologic findings of right ventricular enlargement are:

1. Displacement of the right heart border to the right (PA view).

2. Displacement of a normal sized left ventricle to the left suggesting at first glance left ventricular hypertrophy. (PA view).

3. Straightening, lengthening and possible bulging of the normal concavity between the aorta and left ventricle along the left heart border (PA view).

4. When the right ventricle enlarges, it approaches the anterior chest wall, and since it cannot extend through a rigid structure, it rotates to the left. With further rotation more of its anterior surface appears on the left lateral border (PA view) while the normal left lateral contour is rotated posteriorly and merges into the general cardiac shadow.

5. In the lateral view there is encroachment by the anteriorly expanding right ventricle into the anterior cardiac space; i.e. the space between the anterior aspect of the heart and the sternum.

Right ventricular enlargement occurs secondary to rheumatic valvular disease, (especially mitral stenosis), secondary to left ventricular failure as in hypertension or aortic insufficiency, and in rheumatic myocarditis. Other causes include congenital heart disease as in pulmonic stenosis; chest deformities; A-V fistulas; beriberi; and pulmonary embolism. Many chronic lung diseases such as emphysema and bronchitis produce right ventricular hypertrophy (chronic cor pulmonale) although no cardiac enlargement is noted radiologically.

RIGHT ATRIUM

The right atrium lies to the right of, in a plane with, and somewhat posterior to the right ventricle. In the standard PA film it forms the right heart border. Enlargement of the right atrium is difficult to detect by routine radiologic methods but if often can be visualized in the right anterior oblique projection where its shadow obscures the portion of the retrocardiac space just above the diaphragm. Since the right atrium lies to the right of the esophagus, the barium-filled esophagus in this view will appear to course within the density of the enlarged auricle, apparently transecting it.

Right atrial enlargement is not nearly as common as enlargement of the other chambers of the heart. It is usually a secondary manifestation of right ventricular failure, except when caused by the rare condition of tricuspid stenosis.

CARDIAC AND EXTRACARDIAC CALCIFICATIONS

Calcifications have been noted in small and large arteries, heart valves, intracardiac thrombi, myocardium and pericardium. The cause of the calcification is most commonly secondary to inflammatory or degenerative disease.

1. Valves

Calcification of the valves, in particular the aortic and mitral valves, may occur in both rheumatic and arteriosclerotic heart disease. When only one valve is calcified and there is any question as to which one it is, image intensification, cine films, fluoroscopy, oblique studies, overpenetrated films or body section studies will usually determine its identity. When both the aortic and mitral valves are calcified, the aortic valve lies anterior to the mitral valve in the oblique view and almost directly below it in the lateral view.

FIG. 3.
(A) Unknown 3 — see article.
(B) Unknown 4 — see article.

FIG. 4.
(A) PA View
(B) Pulmonary Angiogram
} Unknown 5

2. Heart Wall

Calcification of the wall of the distended left atrium in mitral valvular disease with insufficiency may often be seen on body section studies (tomograms).

3. Vessels

Calcification of the coronary arteries may be seen at fluoroscopy and identified on cinefluorograms.

Calcification of the aortic arch in many individuals past middle age may be visualised as a shell just inside the margin of the aortic knob. Calcification of the ascending aorta is often syphilitic in origin and the walls of aneurysms, etiologically either arteriosclerotic or syphilitic, may also show calcium.

THE PERICARDIUM

The pericardium, a closed fibrous sac, consists of visceral and parietal layers which are reflected on each other. Rapid accumulation of fluid such as occurs in hemorrhage or purulent pericarditis results in compression of the heart and cardiac tamponade.

Slower distension, usually the result of inflammation, can distend the pericardium to accommodate several litres of fluid. Pericardial effusions of 300 c.c. or less are seldom diagnosed since the heart contours themselves will not be changed. The significant radiologic features of a major pericardial effusion are:

1. An enlarged globular boggy cardiac outline with hazy margins, and marked and equal enlargement both to the right and left. (PA view).
2. Sudden onset when compared to previous films.
3. Presence of a dilated superior vena cava.
4. The finding of cardiac pulsations which are markedly diminished at fluoroscopy.
5. Epicardial fat lines seen on cinefluoroscopy.

Probably the most significant evidence for pericardial effusion is progressive day to day change in the cardiac contour, the size of the cardiac shadow either increasing or diminishing. The more frequent causes of pericardial effusions are rheumatic fever, tuberculosis, myocardial infarction, uremia, metastatic growths involving the pericaridum, trauma, and rupture of an aortic or dissecting aneurysm.

In constrictive pericarditis, "the small still heart" is seen only in patients with advanced and uniform constriction. Most patients with early obliterative or partially constricting pericarditis do not have such findings. For example, the heart may be diminished in size or may be enlarged. At fluoroscopy, pulsations may be diminished on the right or at the base of the heart, while those at the apex on the left remain normal or are even exaggerated.

CASE HISTORIES

Case 1 — (Figure 1B)

This 49 year old woman was admitted with a 4 month history of substernal tightness followed by dyspnea in the latter weeks. The left chest in the lower 2/3 was dull to percussion and had decreased air entry. The heart was enlarged to the anterior axillary line. The PA film reveals a considerably enlarged cardiac silhouette, globular in shape with hazy outlines. This is consistent with pericardial effusion but a definite diagnosis cannot be made by this film alone. A subsequent pericardial aspiration removed 40 cc of bloody fluid containing some abnormal cells. The final diagnosis confirmed at autopsy was secondary carcinoma of the pericardium with large pericardial and pleural effusions.

Case 2 — (Figure 2B)

This 73 year old woman was admitted with a history of increasing weakness, dizzy spells and fainting of 3 months duration. Two years previously she was admitted with rheumatic heart disease, both mitral stenosis and insufficiency. The lateral film reveals an enlarged heart with striking enlargement of the left atrium which shows unusual prominence posteriorly. The arrow indicates the direction of left atrial enlargement. Note also that the retrocardiac space has been completely obliterated by the enlarged atrium. The ring like calcification seen in the wall and roof of the left atrium, and the enlarged left atrium are compatible with mitral valvular disease.

Case 3 — (Figure 3A)

This 42 year old male was admitted for insertion of a mitral Starr-Edwards' valve for known severe mitral stenosis and insufficiency. The P-A film shows a grossly enlarged heart with marked enlargement of the left atrium. The atrium can be almost seen with a contrast material density superimposed on the cardiac silhouette enlarging the heart to the left and the right. In addition there is some prominence in the main pulmonary vessels suggesting a degree of pulmonary hypertension.

Case 4 — (Figure 3B)

This 29 year old female was admitted with an eight year history of paroxysmal nocturnal dyspnea, angina decubitus and pain on exertion. Symptoms included marked fatigue and shortness of breath with the slightest exertion. On examination, blood pressure 130/50, heart rate 76 per minute, apex in 6th intercostal space at left anterior axillary line. A grade III/IV diastolic blow was best heard along the left sternal border. The P-A film shows marked enlargement of the heart in the region of the left ventricle. This gives the appearance of the "boot-shaped" heart associated with left ventricular hypertrophy. The radiologic diagnosis of aortic valve disease was confirmed at operation and autopsy.

Case 5 — (Figure 4)

This 36 year old male presented with a 3 month history of dull aching pain and tightness in the retrosternal area aggravated by deep breathing and coughing. The patient suffered multiple left rib fractures when involved in a car accident 3 years ago. The P-A film shows a large grape-fruit like mediastinal mass which is confluent with and appears to have the contours of the aorta. The pulmonary angiogram clearly demonstrates the mediastinal mass to be a huge aneurysm arising from the descending thoracic aorta, the position of which is typical of that seen in traumatic aneurysms. The aneurysm extends almost entirely anteriorly filling the potential space beneath the aortic arch. It is displacing the left atrium inferiorly. Its wall is very thin and there is no evidence of thrombus formation within the aneurysm.

Z. Cohen 6T9

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REFERENCES

1. Squire, Lucy F.: Fundamentals of Roentgenology. Harvard Press, Cambridge, Mass. 1964.
2. Schwedel, J. B.: Clinical Roentgenology of the Heart. Annals of Roentgenology, Vol. XVIII. Harper & Brothers, New York, 1948.

The Role Of Lysosomes in Rheumatology

INTRODUCTION

It is now apparent that lysosomes play a vital role in the pathogenesis of arthritic diseases and indeed, many other varieties of inflammatory disorder. Current research aims for the successful formulation of an elusive 'final common pathway' concept to explain how the initial insult, whatever it may be, results in acute or chronic inflammation leading to eventual tissue degradation and joint destruction. Unfortunately, the results of extensive investigation in this area by immunopathologists have failed to come up with any one, easily understood, unifying hypothesis. Nevertheless, the role of the lysosome *is* becoming clear—it appears to be involved at *some* stage in many or all of inflammatory diseases. The 'inciting' mechanisms of joint disease, whether primarily infective, hereditary, physical, or auto-immune in nature, may operate via any one of a number of different pathways, but secondary involvement of lysosomes may be necessary for the mediation of actual joint inflammation. This paper will review some of the major advances in our knowledge of lysosomes, as revealed in both the experimental pathogenetic model and in the clinical disease state.

THE NATURE AND FUNCTION OF LYSOSOMES

Lysosomes were first described by De Duve in 1955 as specialized subcellular organelles containing hydrolytic enzymes. They are thought to be present in all living cells except red blood cells, even in primitive plant, fungal, and yeast cells. These heterogeneously appearing bodies contain up to 30 hydrolytic enzymes, all exerting maximum activity in the pH range 4.0-5.0. Synthesized in nearby ribosomes, these 'acid hydrolases' are capable of breaking down all the major constituents of living things (proteins, carbohydrates, fats, and nucleic acids), if released through the lysosomal membrane into the cytoplasm of the cell, or into the extracellular environment. Two well known functions of lysosomes are: autolysis during cell necrosis; and intracellular digestion. Foreign particles are ingested during *endocytosis* (phagocytosis) and the endocytic vacuoles so formed are called *phagosomes*. *Primary lysosomes* then may merge with the phagosomes and discharge enzymes into them, forming *secondary lysosomes* or *phagolysosomes*. Indigestible material not extruded from the cell by *exocytosis* remains as a *residual body*. If the cell is subjected to minor trauma, ischemia, or lack of nutrients, particles of its *own* cytoplasm may be degraded by its *own* lysosomal enzymes, the cell nevertheless remaining viable. This activity takes place in *autophagic vacuoles* and is known as *autophagy*.

LABILIZATION OF LYSOSOMES

Agents impairing lysosomal membrane integrity (thereby *labilizing* the enzymes within the lysosome) provoke inflammation and induce experimental arthritis. Easily controlled models of lysosomal disruption result in useful observations concerning the sequence of events in lysosomal mediation of inflammation. Well established models include:

(a) Injections of streptolysins A and O and alpha-staphylococcal toxins when introduced into skin or joint induce immediate inflammation due to disruption of lysosomes. Mitochondria are not affected. With repeated intra-articular injection of streptolysins, a chronic, sometimes villous synovitis results with hypertrophy of lining cells, infiltration of synovium by plasma cells and lymphocytes, pannus formation and cartilaginous erosion[1,2]. This is very similar to the picture seen in chronic Rheumatoid Arthritis.

(b) Hypervitaminosis A promotes the release of cartilage-degrading proteases from chondrocyte lysosomes *in vivo* and *in vitro*[3].

(c) Sodium urate and other microcrystalline substances labilize leukocyte lysosomes by stimulating the rapid merger of primary lysosomes with phagosomes[4].

(d) Physical factors include: hypotonic conditions, freezing and thawing, low pH, X-ray and UV-irradiation, ischemia, and anoxia.

(e) Certain steroids like progesterone, testosterone, DOC and diethylstilboestrol.

(f) Immune reactions:

(i) Antibodies formed against crude extracts of liver lysosomes produce labilization of lysosomes within living fibroblasts[5].

(ii) Heterologous antibodies to mouse tissue produce changes in tissue cultures of cartilage which closely resemble those brought about by lysosomal effects of hypervitaminosis A[6].

(iii) Antibodies to purified leukocyte lysosomes can induce the degranulation of other leukocytes[7].

(iv) A suspension of leukocytes that had ingested the complex formed by the interaction of Rheumatoid Factor and reactant gamma-G globulin,

released lysosomal enzymes from granular form into the surrounding medium[8].

(v) In models of delayed hypersensitivity, macrophages of sensitized animals are injured when their lysosomes take up challenge doses of antigen[9].

THE EFFECTS OF LYSOSOMAL ENZYMES ON JOINTS

Several prominent leukocytic lysosomal enzymes are known to induce articular inflammation when suitably injected. These include:

(1) a cationic protein acting by disruption of mast cell granules[10].

(2) A protease inhibited by epsilon-aminocaproic acid which induces capillary permeability and acts as a fibrinolytic agent[11].

(3) Cathepsins capable of breaking down the protein polysaccharide of cartilage matrix. The same enzymes are present in cartilage lysosomes themselves.

Of course, polymorphonuclear leukocytes entering the joint spaces from the blood, are not the only source of lysosomal hydrolases in the joints. Synovial lining cells, cartilage cells, wandering and fixed macrophages and vascular pericytes also contain lysosomes. The former two cell types contain hyaluronidase, collagenase, and the tissue activator of plasminogen, all of which can contribute to local tissue injury (Plasmin can degrade cartilage matrix).

STABILIZATION OF LYSOSOMES-THERAPEUTIC AGENTS

Many current therapeutic agents used to alleviate joint inflammation do so by stabilizing lysosomes which would otherwise be disrupted by the noxious stimuli discussed above.

Direct lysosomal *membrane* stabilization is thought to be an important anti-inflammatory action, both *in vitro* and *in vivo,* of adrenal corticosteroids (and their synthetic analogs), and also salicylates and choloroquine[12 13]. Inorganic gold salts, on the other hand, are selectively taken up and concentrated by macrophage lysosomes, where they are thought to directly inhibit enzyme activity. Indomethacin inhibits the migration of leukocytes in crystal-induced inflammation, suggesting that lysosomal products of white cells may be thereby prevented from reacting at the local inflammatory site. Colchicine apparently inhibits the merger of membranes of endocytic vacuoles with the pre-existent primary lysosomes. This agent has no direct effect on lysosome membrane permeability[14]. Finally, phenylbutazone is thought to act by inhibiting the release of lysosomal enzymes into the circulation, in intact animals, but there is no effect on isolated lysosomes[15].

Although the above stabilizing effects have been observed, the actual biochemical mechanisms producing the effects remain unknown.

CLINICAL CORRELATES

Clinical studies in patients with Rheumatoid Arthritis have revealed that erosion of cartilage matrix in this condition appears to be due to the release of lysosomal enzymes principally from inflammatory cells of the invading pannus (perhaps also from cartilage itself) with degradation of cartilage protein polysaccharide. This strongly resembles the picture observed after experimental injection of excess Viatmin A. We have also seen how the chronic synovitis, cellular infiltration, pannus formation and cartilaginous erosion of this condition was mimicked by experimental injection of bacterial toxins. As well, the synovial tissue contains macrophage-like cells filled with residual bodies and autophagic vacuoles—each bearing witness to lysosomal activation[16]. Rheumatoid synovium and synovial fluid contain higher than normal levels of cathepsins, acid phosphatase, and beta-N-acetylglucosaminidase, presumably released from either locally inflammed synovium or from immigrant polymorphs. Interestingly, there is no increase in *alkaline* phosphatase, an enzyme also present in white blood cells. This *may* indicate that the majority of acid hydrolases arise from cells within the synovium or from the synovial lining itself.

Some of the polymorphs seen in this condition have been labelled 'RA cells'. These are leukocytes that have engulfed rheumatoid factor and its reactant (discussed in another article in this issue) from synovial fluid exudate. Presumably, the phagosomes so formed merge with pre-existent lysosomes and the resulting degranulation and extracellular release may be one pathway explaining the increased levels of the above-mentioned enzymes[17].

The model of microcrystalline sodium urate-induced arthritis is mediated by polymorphonuclear leukocytes. Many of these crystals are too large for the leukocyte to vacuolize, and the unsuccessful attempt at phagocytosis results in the escape of many of the enzymes. Such a mechanism might also explain the crystal-induced arthritis of gout (urate), pseudogout (calcium pyrophosphate) and other experimental arthritides (orotate, calcium oxalate etc.)

Cartilage from osteoarthritic patients has an increased protein to polysaccharide ratio, possibly due to the action of hyaluronidase attacking from the serum. This enzyme cannot be demonstrated in cartilage itself. Similar findings are produced experimentally by introduction of lysosomal extracts and in hypervitaminosis A.

SIGNIFICANCE OF LYSOSOMES

It is thus likely that lysosomes of synovium, polymorphonuclear leukocytes and perhaps those of cartil-

age cells, when acted upon by any of a large number of labilizing agents, release enzymes that contribute to the pathogenesis of rheumatoid arthritis, crystal-induced arthritis, and perhaps osteoarthritis. Ideally, the therapeutically minded rheumatologist should seek to elucidate more fully the nature of and factors responsible for production of the noxious agents affecting joint cells containing lysosomes. Unfortunately, it seems impossible that these many factors can be prevented from either forming, or once formed, acting on cellular lysosomes to produce damage. It is tempting to consider that antigen-antibody complexes may be important labilizing agents in diseases like Rheumatoid Arthritis. It is equally possible that antigen-antibody complexes are a *result* of lysosomal disruption and subsequent production of degraded molecules acting as antigens. This hypothesis was set forth by Weissmann[18] in an attempt to explain how RA characteristically demonstrates *continued* autoantibody production. He reasoned that there must be a *continued* elaboration of autoantigens, somehow brought about by a continuing, episodic denaturation of normal host tissues. He noted that synovial cells, which contain prominent residual bodies and autophagic vacuoles, are designed to remove and process foreign antigens. The auto-antibodies of RA may be formed when materials found in phagolysosomes or autophagic vacuoles of those cells with intense endocytic activity, are presented to antibody-forming cells in the same way as are hetero-antigens. Antibodies (and complement) so formed could then react with the antigen, as well as with normal antigenically similar tissues, to produce the changes observed in the polymorphs of synovial fluid, and possibly, a host of other deleterious effects on normal tissues.

A generalized scheme summarizing these events follows:

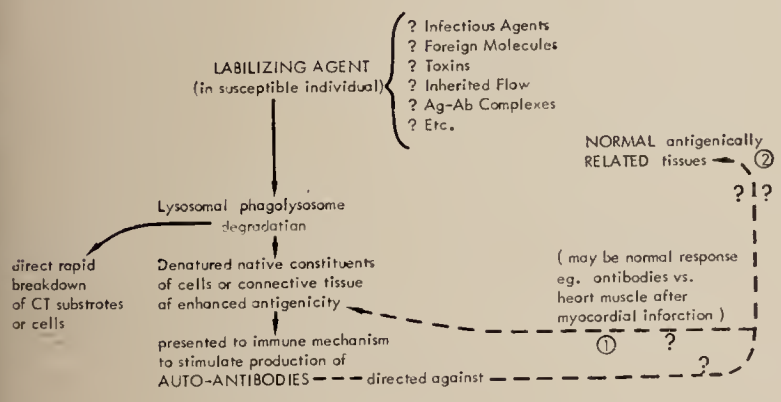
LABILIZING AGENT
(in susceptible individual)
? Infectious Agents
? Foreign Molecules
? Toxins
? Inherited Flow
? Ag-Ab Complexes
? Etc.
NORMAL antigenically RELATED tissues
② ? ! ?
Lysosomal phagolysosome degradation
direct rapid breakdown of CT substrates or cells
Denatured native constituents of cells or connective tissue of enhanced antigenicity
(may be normal response eg. antibodies vs. heart muscle after myocardial infarction)
① ? ?
presented to immune mechanism to stimulate production of AUTO-ANTIBODIES
directed against

FIG. 1.
Auto-immune Hypothesis of Joint Disease
(Modified after Weissmann[18])

Probably the different arthritides have, more or less, different cells involved and respond to different labilizing or stabilizing agents. For example, in RA, lysosomes of synovial cells may be primarily involved with polymorphs and macrophages only secondarily, and the major injurious agent may be an immune complex. On the other hand, foreign molecules, toxins, PPLO, viruses etc., may be involved in individual cases. Leukocyte lysosomes may be the primary targets for bacterial or crystal-induced arthritides, while chondrocytic lysosomes may be the target in osteoarthritis.

It is thus obvious that the exact pathway followed by the immune process is far from clear. However, a common pathway (not necessarily "final") involving lysosomes does appear clear: Endocytosis —> inappropriate release of inflammatory materials —> further leukocytic infiltration —> joint injury and cartilage degradation[19]. Unfortunately the agents or events actually *initiating* the pathologic process in the previously normal individual remain unknown. It is certainly unlikely that circulating autoantibodies are initially responsible; it is more likely that some form of minor local trauma occurring in an individual with an inherited tendency towards a weak homeostatic immune mechanism is at fault. Such a vague conclusion at this time seems to be the safest.

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REFERENCES

1. Weissmann, G.; Becker, B.; Wiedermann, G. and Bernheimer, A. W.: Amer. J. Path. 46: 129, 1965.
2. Pras, M. and Weissmann, G.: Arthritis Rheum. (Abstract) 9: 533, 1966.
3. Fell, H. B. and Dingle, J. T.: Biochem. J. 87: 403, 1963.
4. Phelps, R. and McCarty, D. L. Jr.: J. Exp. Med. 124: 115, 1966.
5. Weiss, L. and Dingle, J. T.: Ann. Rheum. Dis. 23: 57, 1964.
6. Fell, H. B. and Weiss, L.: J. Exp. Med. 121: 551, 1965.
7. Quie, P. G. and Hirsch, J. G.: J. Exp. Med. 120: 149, 1964.
8. Astorga, G. and Bollet, A.: J. Arthritis Rheum. 8: 511, 1965.
9. Norton, W. and Ziff, M.: Immunology 8: 81, 1965.
10. Janoff, A. and Zweifach, B. W.: J. Exp. Med. 120: 747, 1964.
11. Weissmann, G. and Thomas, L.: Recent Progr. in Hormone Res. 20: 215, 1964.
12. Weissmann, G.: New Eng. J. Med. 273: 1084, 1143, 1965.
13. Miller, W. S. and Smith J. G.: Proc. Soc. of Exper. Biol. Med. 122: 634, 1966.
14. Rajan, K. T.: Nature 210: 959, 1966.
15. Barland, P.; Novikoff, A. B. and Hamerman, D.: Amer. J. Path. 44: 853, 1964.
16. Wyllie, J. C.; Haust, M. D. and More, R. H.: Lab. Invest. 15: 519, 1966.
17. Zucker-Franklin, D.: Arthritis Rheum. 9: 24, 1966.
18. Weissmann, G.: Lancet 2: 373, 1964.
19. Weissmann, G.: Arthritis Rheum. 9: 834, 1966.

Dr. Philip Hench

"Rheumatism"—The very name has always conjured up visions of a slowly progressive, intractable, crippling disease. And until recently there was very little the medical profession could do to alleviate the victim's incapacity or discomfort. However, a breakthrough finally occurred—the use of corticosteroids—and it is for this work that Dr. Philip Hench was awarded the 1950 Nobel Prize in Medicine and Physiology (jointly with Dr. E. C. Kendall and Prof. T. Reichstein).

Philip Showalter Hench was born in Pittsburgh, Pennyslvania in 1896. He obtained his B.A. at Lafayette College and entered the University of Pittsburgh School of Medicine, receiving his M.D. degree in 1920. In 1921 he became a fellow of the Mayo foundation, the graduate school of the University of Minnesota's Dept. of Medicine. He entered the Mayo Clinic in 1923 and began his career in the field of Rheumatology.

Even as a neophyte in this field he had a number of experiences that drastically altered his beliefs and approach toward Rheumatoid Arthritis, and in fact would later alter the ideas of the entire medical world. One of these occurred during the era when rheumatic therapy included the induction of febrile reactions by the injection of protein, in the belief that this sometimes produced remissions.

> "One day a badly disabled rheumatoid patient reacted promptly and with unusual effectiveness to the protein injection; seemingly a remission of marked degree had been induced. The remission was largely sustained and through the year I have seen the patient frequently and he has had little or no arthritic activity. . . . I have never been able to discount or forget this event."

Another instance which stuck in his mind:

> "On April 1, 1929, a sixty-five year old patient at the Mayo Clinic told me an unusual story. A few days before that date he was painfully affected by Rheumatoid Arithritis as he had been for four years. Then jaundice developed and within a week most of his arthritic manifestations disappeared. The jaundice lasted for five weeks but the rheumatoid arthritis did not relapse until several weeks after jaundice had disappeared."

These events precipitated Hench to think, "Instead of being relentlessly progressive, this disease may be potentially reversible", and he began to search for the ameliorating agent—"nature's dramatic antidote".

It was also apparent that pregnancy sometimes temporarily checked the disease. Past literature had occasionally noted this phenomenon and by careful recordkeeping this was shown to be the case in many instances. It was also noted that pregnancy (and jaundice) sometimes relieved non-rheumatic conditions such as hay fever, asthma, migraine and psoriasis.

What did this mean? Probably there was some common denominator to jaundice and pregnancy. But what? People tried bilirubin, and various and sundry other things found to be abnormal in jaundice—to no avail.

> "It seemed logical to suppose that what caused the relief of rheumatoid arthritis in pregnancy and jaundice were closely related if not identical."

In time, after empirically trying many agents and measures, Hench conjectured that the anti-rheumatoid factor "X" might be an adrenal hormone. He discussed this with his biochemical colleague, Dr. E. C. Kendall, who had succeeded in separating adrenal cortical hormones into six different fractions. In 1941 they decided to try compound E (later renamed cortisone by Kendall and Hench). However, fate prevented the application of this idea for seven years; so great were the problems of isolating the compound that it took this long to obtain sufficient amounts of compound E for human trial. In the interim, their belief that adrenal cortical substances were involved was strengthened by the discovery that various physiological states—anaesthesia, starvation and febrile reaction—which had been

shown to give temporary remission of rheumatic symptoms, also stimulated the adrenal cortex.

On September 21, 1948—the fateful day—Hench began clinical trials of compound E on fourteen patients.

> "But despite our sustained desire to use this hormone, we had no firm conviction, only hope, that this compound might be the mysterious compound X."

The first patient was a woman badly crippled with rheumatoid arthritis in whom they had tried and failed to induce jaundice by oral lactophenin. To their delight, there was a rapid and progressive remission of her subjective, clinical and biochemical symptoms following the injection of compound E. In fact she went shopping a few days after the initiation of therapy. This was astounding, considering the fact that she could hardly comb her own hair before the treatment. It was also noted that there was a fall of the sedimentation rate with the therapy, surely an indication that there had been some biochemical change produced by the therapy.

The results were overwhelming, and even more value was placed on compound E's powers when thirteen other patients also showed remissions on therapy (and return of some or all of the features of the disease on removal of the drug). In addition to compound E studies, Hench also carried out some ACTH studies which proved to be equally successful. However, neither drug was a cure! They were apparently able to "correct (at least temporarily) the abnormal pathologic physiology underlying rheumatoid arthritis, at any stage of the disease, and to bring its active symptoms under control, in other words, 'put out the fire'. . . . However, while they were the fireman that puts out the fire, they were not the carpenter that rebuilds the damaged house."

On October 26, 1950, the announcement came that the Swedish Caroline Institute of Medicine had awarded the Nobel Prize in Medicine to Drs. Kendall, Hench and Reichstein for their research in the field of adrenal cortical hormones (Hench shared his part of the award with Drs. Slocumb and Polley, his associates at the Mayo Clinic). The recipients were well chosen; their discovery, while unable to cure this dread disease, had given medicine a very effective tool, not only against rheumatic diseases, but also against other immunologic or allergic diseases. Hench was aware of its possible applications and, as he pointed out in his Nobel lecture,

> "Whatever the immediate or future destiny of these hormones may be in the field of practical therapeutics, they already (in 1950) have demonstrated clearly the potential reversibility of many diseases that had been heretofore thought to be more or less relentlessly progressive. In particular they constitute powerful tools with which we can investigate many problems related to the etiology and treatment of a wide variety of diseases."

In the years following this discovery Hench has continued his activities in medical and research organizations. He was associate in the division of medicine and then staff consultant and head of the Department of Rheumatic Diseases at the Mayo Clinic, and also a professor at the Mayo Foundation. Dr. Hench retired from the Mayo Clinic in 1957 and died on March 31, 1965 of pneumonia and diabetic coma. But on re-examining his life and work we see the truth of Theoreli's statement (Nobel Festival, 1947), "The physiology of today is the medicine of tomorrow."

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REFERENCES

1. Current Biography, 1950, (230).
2. Annals of Rheumatic Diseases 8; 90-96 (1949).
3. Journal of the American Medical Association; 144; 1327 (1950).
4. New York Times, April 1st, 65, p. 35.

Clinicopathological Conference

Congestive Heart Failure And Abnormal Serum Proteins In A Seventy-seven Year-old Female

CASE PRESENTATION

A 77 year old white woman gave a history of excellent health throughout her life until December, 1962 when she developed gradually progressive swelling of both ankles and was admitted to hospital for investigation. No specific cause for her oedema was found but she was found to have an anemia (Hb 7.2 gm.%). The WBC was 2400 (with 53% lymphocytes), and platelet count was 120,000. The ESR was 141 mm./hr.

Stools were negative for occult blood, upper gastrointestinal radiography showed only a small hiatus hernia. A trial injection of vitamin B12 produced no significant reticulocytosis nor rise in hemoglobin.

Two months later in February, 1963, the patient was re-admitted to hospital for further investigation. She was still experiencing intermittent swelling of the ankles late in the day and moderate shortness of breath on exertion. She also complained of gradually progressive fatigue, weakness, and moderate anorexia. She reported no weight loss, fever, chills or sweats. She had noticed no skin rashes, or bruising tendency but did report several brief episodes of epistaxis over several months prior to admission. There were no other symptoms.

Physical examination on admission revealed a rather pale, thin, elderly woman in no apparent discomfort. There was conjunctival and oral pallor but no icterus. Moderate arteriolar narrowing was seen in the optic fundi. The jugular veins were distended 5 cm. above the sternal angle. The chest was clear to percussion, but fine basal rales were heard bilaterally. The heart rate was 64 per minute and regular; the apex beat was felt in the sixth intercostal space just lateral to the midclavicular line, and a Grade II/IV harsh pansystolic murmur was heard maximally at the apex. The blood pressure was 180/80 and all peripheral pulses were present. A firm, smooth liver edge was palpable two inches below the right costal margin on deep inspiration. The splenic tip was hard and blunt and descended one inch below the left costal margin on inspiration. Rectal examination was unremarkable. There were several small, firm, non-tender, mobile lymph nodes, palpable in both anterior cervical chains and in the right axilla. There was no bone tenderness. The skin was normal except for pallor and a few small ecchymoses on the left leg. There was bilateral 1+ pitting oedema of the ankles. Neurological examination was normal except for symmetrically diminished reflexes in the legs.

Laboratory investigations showed the following: Hemoglobin 6.9 gm.%, hematocrit 21%, MCHC (mean corpuscular hemoglobin concentration) 33%, and the blood film showed marked rouleaux formation with increased background staining. The WBC was 2000 with 65% lymphocytes, 30% neutrophils, 2% band forms, 2% monocytes and 3% eosinophils. Reticulocytes were 4% and platelets 88,000. The ESR was 146 mm/hr. Urinalysis was essentially normal; there was no bile but a trace of urobilin was present. The serum bilirubin was 0.5 mg.%, SGOT 10 units, alkaline phosphatase 31 I.U., BSP retention 3.5% at 45 minutes, CCF negative, and thymol turbidity 1.5 units. Serum calcium was 9.5 mg.%. The bleeding time was 6 min., the clotting time 8 minutes 15 seconds, prothrombin time 13 seconds, OSPT (one stage prothrombin time) normal, and TGT (thromboplastin generation time) decreased. Serum proteins were 8.5 gm.%, with 2.3 gm.% albumin and 6.2 gm.% globulin. The Wasserman and Coombs tests were negative. No cryoglobulins were detected in the serum after 48 hrs., but the SIA test was positive.

Serum protein electrophoresis showed normal albumin, alpha 1, alpha 2, and beta globulins, but decreased gamma globulin and a markedly elevated and broad gamma 2 peak of 4.4 gm.%. A test for L.E. cells was negative. Two attempts at bone marrow aspiration produced only scanty aspirate comprised of granulocyte and erythroid precursors. Some 90% of the cells resembled "mature lymphocytes". A lymph node biopsy done at this time is described under "Pathology".

Ultracentrifugation of the patient's serum showed 4.2 gm.% albumin, 1.6 gm.% 7Sglobulin, and a total macroglobulin fraction of 6.15 gm.%, comprised of; 4.9 gm.% 17 S, 1.0 gm.% 25S, and 0.34 gm.% 30S.

ECG was unremarkable. Chest X-rays showed evidence of old tuberculous disease in addition to cardiomegaly and manifestations of congestive heart failure. A skeletal survey showed only mild generalized osteoporosis.

During this hospitalization 6000 ml. of plasma were removed by plasmapheresis but this produced no significant change clinically or in the serum electrophoretic pattern. The signs of congestive failure improved following treatment and she was discharged on penicillamine 700 mg. t.i.d., and hydrochlorthiazide 500 mg. daily. She was to be followed in the out-patient's department.

Over the next month she was also started on prednisone, 30 mg/day in an attempt to improve her marrow function. However, in April 1963, she was again hospitalized with clinical and radiological evidence of bilateral basal pneumonia. She was found to have hepatomegaly (but not splenomegaly). Multiple small anterior cervical lymph nodes, left supraclavicular nodes, and bilateral axillary nodes were present as well. The hemoglobin was 7.5 gm. %, WBC 4600 with a shift to the left and platelets 70,000. Serum proteins were 6.7 gm.% with 1.5 gm. % albumin and 5.2 gm. % globulins; the serum electrophoretic pattern was unchanged. The dose of prednisone was increased and the pneumonia responded well to treatment with penicillin. Penicillamine 1200 mg./day was given and later chlorambucil 4 mg./day was added. She was finally discharged in June 1963, feeling better, but with no change in her hematological status.

One week later, she was readmitted after becoming rapidly weaker, and unable to care for herself. Her hemoglobin had fallen to 5 gm. % and there was dark red blood in the rectum. The previous lymphadenopathy was unchanged, but neither liver nor spleen were palpable. There were numerous petechiae scattered over the anterior abdominal wall. The WBC was 1400 (no differential recorded), platelets 47,000, reticulocytes 0.8% and the ESR was 142 mm./hr. Sigmoidoscopy showed the site of bleeding to be internal haemorrhoids. The patient was transfused up to 9.5 gm. % Hb., and prednisone and penicillamine were continued. Barium enema and chest X-ray were unremarkable. The patient's general condition remained poor for 10 days, and then rapidly deteriorated, with steadily rising temperature to 105°F rectally, signs of bilateral pulmonary infection and possible septicemia. The WBC fell to 350 and she died two and one-half weeks after admission, despite therapy with steroids and antibiotics.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis will be discussed under several headings, taking each major manifestation as it was disclosed in the history. The presenting situation was that of chronic congestive cardiac failure.

Chronic cardiac failure can be divided into two broad classes which are termed high output and low output failure. Included in the causes of high output failure are entities like thyrotoxicosis, marked anemia and arterio-venous fistulae. Low output failure can be roughly divided into the failure of;

1. sustained elevated ventricular pressures (eg., systemic or pulmonary hypertension, valvular heart disease)
2. cardiomyopathies (eg., myocardial infarction, infiltration of foreign substances into the myocardium)
3. the cardiac arrhythmias.

The factors at work in the present patient will be further discussed following the pathological findings.

Peripheral blood examination in this patient showed evidence of a generalized myeloid suppression or pancytopenia, that is, there was anemia, absolute neutropenia, and thrombocytopenia.

The pancytopenias can be roughly divided into three categories on the basis of bone marrow findings as;

1. reduced or absent myeloid elements: the aplastic-hypoplastic group (eg., caused by cytotoxic drugs, irradiation)
2. replacement of marrow by non-myeloid elements: the myelophthisic group (eg., carcinomatous metastases to marrow cavities)
3. the pancytopenias with cellular marrow (eg. hypersplenism).

The patient's mild bleeding tendency must be accounted for by abnormalities in vessels and/or platelets because the coagulation time and other more sensitive tests of coagulation factors were normal. The bleeding time gives only a very rough indication of vessel function and problems in this area cannot be ruled out by the finding of a normal value. The platelet count in this patient, though reduced, was not sufficiently low to account for the bleeding reported. However, although the actual numbers of platelets may have been sufficient, some abnormality of platelet function may have been present.

Two other observations from the laboratory data can be considered together, that is, the rouleaux formation and background staining seen in the blood films, and the high ESR (140 mm./hr.), which point to some disturbance of serum proteins. In this case the total proteins are given as 8.5 gm. % with an A/G ratio of 2.3/6.2. A globulin fraction of this magnitude by itself suggests myeloma but, hyperglobulinemia may be found in many conditions and with a positive SIA test reported, such diverse conditions as Kala-azar, systemic lupus erythematosus, and hepatic cirrhosis remain possibilities.

However, when the entire clinical and laboratory picture is assessed, the pancytopenia, the hemorrhagic phenomena, and the abnormal serum electrophoresis, the differential diagnosis comes to center mainly on multiple myeloma and the macroglobulinemia of Waldenstrom.

In multiple myeloma, osteolytic lesions together with bone pain and pathological fractures and renal impairment, are common findings, while hepatosplenomegaly is rare, all in contradistinction to our case. The excretion of Bence-Jones protein as seen in myeloma would perhaps have been helpful if reported, but this

phenomenon is encountered in only 50% of cases of myeloma.

A definitive diagnosis of macroglobulinemia can be made with the aid of two more specific tests, ultracentrifugation and immuno-electrophoresis of serum.

The ultracentrifugation carried out on this patient's serum showed a total macroglobulin fraction of 6.15 gm. % with components mainly in the 19S fraction and smaller amounts of even higher molecular weight globulins (25S and 30S). The diagnosis of macroglobulinemia was thereby proved. At the same time, this patient showed a reduction of the 7S or IgG fraction; which is considered to be the most important in resistance to bacterial infections. This functional hypogammaglobulinemia may account in part for her repeated episodes of lower respiratory tract infection.

The source of these high molecular weight proteins is now believed to be a peculiar form of lympho-plasmoid cell found in cases of macroglobulinemia. In fact the diagnosis of Waldenstrom's macroglobulinemia may be made on finding these abnormal cells in a lymph node biopsy (see below).

The pancytopenia in this patient falls into the myelophthisic group, with replacement of normal myeloid elements by lympho-plasmoid cells. The congestive heart failure can be partly or perhaps wholly explained on the basis of the extremely high plasma viscosity which is usual in these patients.

The underlying proliferation of "lymphoid cells" in Waldenstrom's macroglobulinemia exists in many forms, ranging from benign to markedly malignant with a correspondingly different prognosis. In the more benign forms, few of these plasmoid cells are found, and they are confined to more or less normal lymph nodes. In the most malignant form of this condition it may behave as an aggressive, invasive lymphosarcoma with myeloid replacement and extension outside the lymph nodes. In our case, we see that there is no clinical evidence of widespread malignant dissemination but bone marrow replacement has led to severe pancytopenia. Terminal aggravation of the pancytopenia may reflect either advancing disease or more likely the effect of cytotoxic drugs such as chlorambucil. The correct placing of this case in the benign-malignant scale must await the post mortem findings.

PATHOLOGICAL PRESENTATION

Gross Findings

Petechial hemorrhages were present covering the trunk and to a lesser degree the limbs. There was a large ecchymosis in the right antecubital fossa.

In both lungs there was some fibrosis surrounding multiple granulomata. The epicardium was thickened near the apex over the left ventricle anteriorly. Generalized atherosclerosis was seen in all the great vessels with severe calcification in the iliac arteries.

The liver weighed 1490 gms. and showed minor fatty change. There were three hard, round black stones in the extrahepatic biliary passages, the largest measuring 1.2 cm.

The capsules of the kidneys stripped easily and the surface was moderately granular. The cortex was pale and there was slight streaky medullary calcification.

In the duodenum, there was a nodular thickening in the pyloric ring. Several submucosal cystic pale thickenings containing a milky fluid were scattered along its length. The lower end of the rectum showed several well-defined ulcers, the largest measuring 2 cm. in length.

The cervical lymph nodes were pale and soft but normal in size. The mediastinal and para-aortic nodes were greatly enlarged and contained mottled areas with a pale pinkish appearance. Smaller but similar nodes were seen around the pyloric end of the stomach, around the pancreas, in the small bowel mesentery, in the porta hepatis and along the brim of the pelvis. Axillary and inguinal nodes were unremarkable.

Slight osteoporosis of the sternum and spinal column was seen. The marrow was uniformly dark red and had an unusual appearance.

Microscopic Findings

Fibrosis was seen in the lung sections. There was marked thickening of the media and intima of many small arteries. Focal emphysema was seen in all areas but particularly in the left upper lobe where there were also areas of bony and myeloid formation, the cellular elements being predominantly lymphocytes and plasma cells.

Sections of the heart showed focal areas of myocardial fibrosis. The mitral ring appeared calcified with some hyalinization.

Sections of liver showed normal parenchymal architecture but infiltration by medium-sized, slightly atypical lymphocytes and plasmoid cells. (see Fig. 1.) In the sections of spleen there was congestion, septal fibrosis and hyalinization of small vessels. The sinusoids and pulp contained large numbers of plasmoid cells. Numerous PAS positive, round bodies were seen in the interstitial tissue and some within the cytoplasm of plasmoid cells.

Both kidneys showed fibrotic thickening of the capsule. There was cortical scarring with chronic inflammatory cell infiltration, more marked in the left.

Stomach sections showed marked hypertrophy of the muscle coat. Scanty infiltrates of eosinophils and plasma cells were seen in the submucosa.

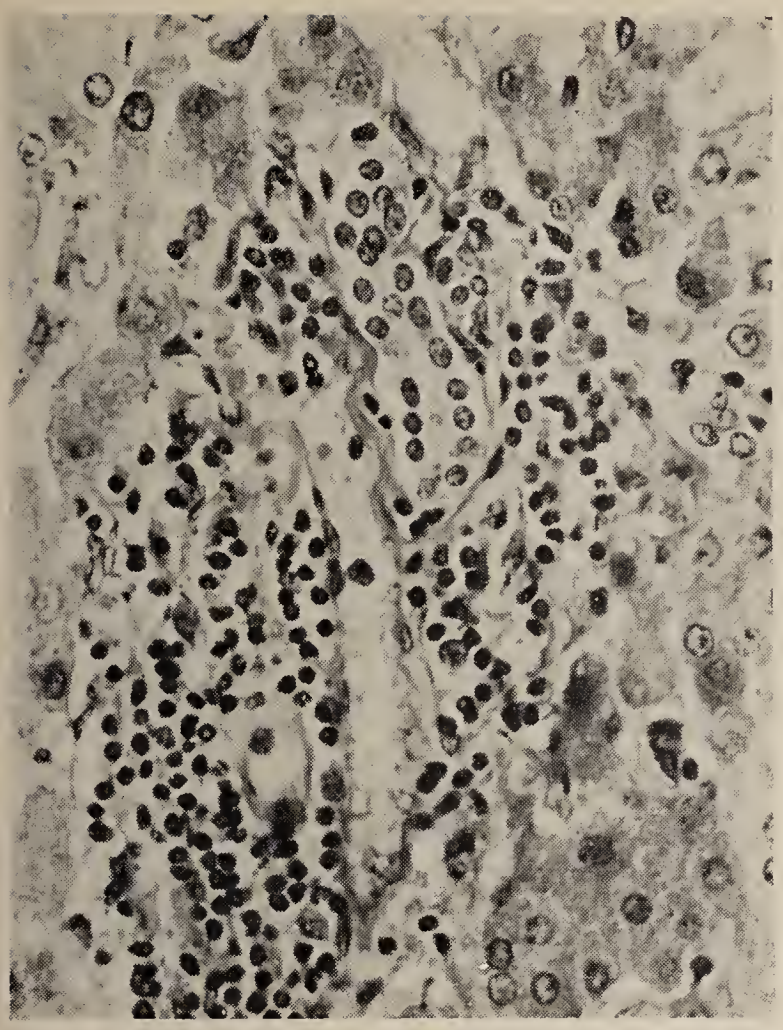

FIG. 1. Periportal infiltration of abnormal plasmoid cells. (liver X430 PAS)

Sections of the rectum showed recent ulceration of the mucosa with necrosis of the submucosa. In and around the ulcers was an inflammatory infiltrate formed by plasmoid cells.

Examination of lymph nodes at autopsy and also the lymph node biopsy showed alteration of the normal architecture. The germinal centres were small and few and the lymphatic channels were dilated. Portions of the nodes were replaced by ill-defined aggregates of lymphocytes. In other areas there were sheets of plasmoid cells. Some abnormal cells were seen extending beyond the confines of the nodes.

The brain sections revealed marked hypercellularity with a few fatty cells. The cells were mostly large atypical lymphocytes and plasmoid cells.

In summary, the lymph nodes, spleen, bone marrow, liver, lungs and rectum showed an infiltration by atypical lymphocytes or "plasmoid" cells of the type described in cases of Waldenstrom's macroglobulinemia.

DISCUSSION

Waldenstrom's macroglobulinemia is a disorder characterized by a great increase in the concentration of macroglobulins in the blood. It is associated with a generalized lymphadenopathy with a pleomorphic infiltrate in the marrow and lymph nodes and focal infiltrations in other organs. The infiltrate consists mainly of "lymphoid" cells (which may be concerned in synthesizing the macroglobulins).

The excess of macroglobulin increases the viscosity of the plasma and is associated with reduced synthesis of antibodies and impaired activity of the clotting factors. It also facilitates rouleaux formation and is responsible for the characteristic elevation of the ESR. "Sludging" of the blood may occur and resultant vascular stasis and anoxia may cause endothelial damage. Impaired activity of clotting along with endothelial damage often resulting in a bleeding tendency.

The disease mainly affects the elderly. It is uncommon but the exact incidence is unknown.

Perivascular infiltrations and vascular changes have been reported as causative agents of the usually typical retinopathy and also a variety of neurological disturbances. Several cases have been reported with miliary lung infiltrations.

The pancytopenia may manifest itself in increased bleeding due to thrombocytopenia and also in an increased susceptibility to infection related to the leukocytopenia. The cause of death in this patient (i.e. pneumonia) appears consistent with this concept. The increased susceptibility to infection may also be related to the functional hypogammaglobulinemia. This is regarded as the primary factor in the severe infections of many patients who do not have a leukopenia.

The course of the disease is variable. However, rapid fatal progression of the neutropenia is inevitable at some stage.

The most common manifestations are marked pancytopenia, repeated minor epistaxes, visual disturbances, cardiac failure, and increased susceptibility to infection. Cerebral complications, infection or cardiac failure may be the cause of death.

Some confusion has arisen between this condition and multiple myeloma, since some patients with Waldenstrom's disease may excrete Bence-Jones protein. Recent studies of the gamma globulins, using ultracentrifugation and immunoelectrophoresis (see below), have aided greatly in clarifying these observations. Five classes of gamma globulins are believed to exist; i.e. IgG, IgA, IgM, IgD and IgE. All are composed of "heavy" (H) and "light" (L) chains with the basic formula H2L2. IgG and IgA are usually 7S monomers (H2L2) while IgM probably exists as a stable 19S pentamer (H2L2)5. Each of these immunoglobulins is present in healthy individuals. It is believed that in neoplasias of lymphoid tissue clones of cells develop which have limited immunological potentialities and synthesize large quantities of one homogeneous protein, as in multiple myeloma or in Waldenstrom's disease.

Normal serum contains about 80 mg. per 100 ml. of macroglobulin (IgM). Moderate "reactive" increases of

the IgM fraction, usually less than 500 mg. per 100 ml. serum, may occur in association with hemolytic anemias of the cold antibody type following atypical (mycoplasma) pneumonia, rheumatoid arthritis, cirrhosis of the liver, lupus erythematosus, infectious mononucleosis, syphilis, occasionally in chronic lymphatic leukemia, lymphosarcoma, carcinoma and even in apparently healthy elderly people. In contrast to this, the IgM fraction in Waldenstrom's disease frequently exceeds 1 gm. per 100 ml. In rare cases (cold hemagglutinin syndrome) the IgM has antibody activity.

Treatment of these patients must involve consideration of the macroglobulinemia, the anemia and the underlying proliferation of "lymphoid" cells.

In dealing with the macroglobulinemia directly, it has been found that penicillamine (a sulphydril containing compound) exerts a depolymerizing effect upon the macroglobulin which results in a decreased blood viscosity. Plasmapheresis is also transiently effective. Both of these methods are limited, however, in that they do not affect the primary process.

It has been found that corticosteroids can exert a stimulatory effect upon the marrow and thus may be used as a symptomatic therapy for the anemia in these conditions.

Cytotoxic agents, chiefly chlorambucil, have been used with reasonably good results in dealing with the proliferative elements of the disease. Reports have shown that treatment with chlorambucil, given over a period of six months, results in substantial decreases in both the plasma macroglobulins and the cellular infiltrates.

The diagnosis of macroglobulinemia should be considered in elderly people showing any of the clinical features mentioned, whenever rouleaux formation and very high ESR's are seen. Measurement of the total serum proteins, electrophoretic examination of the serum for evidence of a dense narrow band in the gamma region, SIA test and estimation of serum viscosity are useful screening tests. Immunoelectrophoresis studies and ultracentrifugation are necessary to identify and measure the immunoglobulin. An adequate specimen of marrow is essential for showing the cytological features of the infiltrate, and lymph node biopsy may be needed if marrow aspiration proves unsatisfactory.

(Immunoelectrophoresis is a technique which combines electrophoretic separation of serum proteins in agar gel with subsequent precipitation of each Ig class by specific anti-globulin sera prepared in animals by injecting human sera).

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REFERENCES

1. Waldenström, J.: Macroglobulinemia. Advances in Metabolic Diseases. 2: 146-58, 1965.
2. Zinneman, H. et al: Macroglobulins and the Sia water test. American Journal of Clinical Pathology, 45: 306-12, Mar. 1966.
3. Dameshek, W.: What is Waldenström's Macroglobulinemia? Acta. Med. Scand., 179: Suppl. 445, 1966.
4. Waldenström's Macroglobulinemia: British Medical Journal, 5427: 73-4. Jan. 1965.

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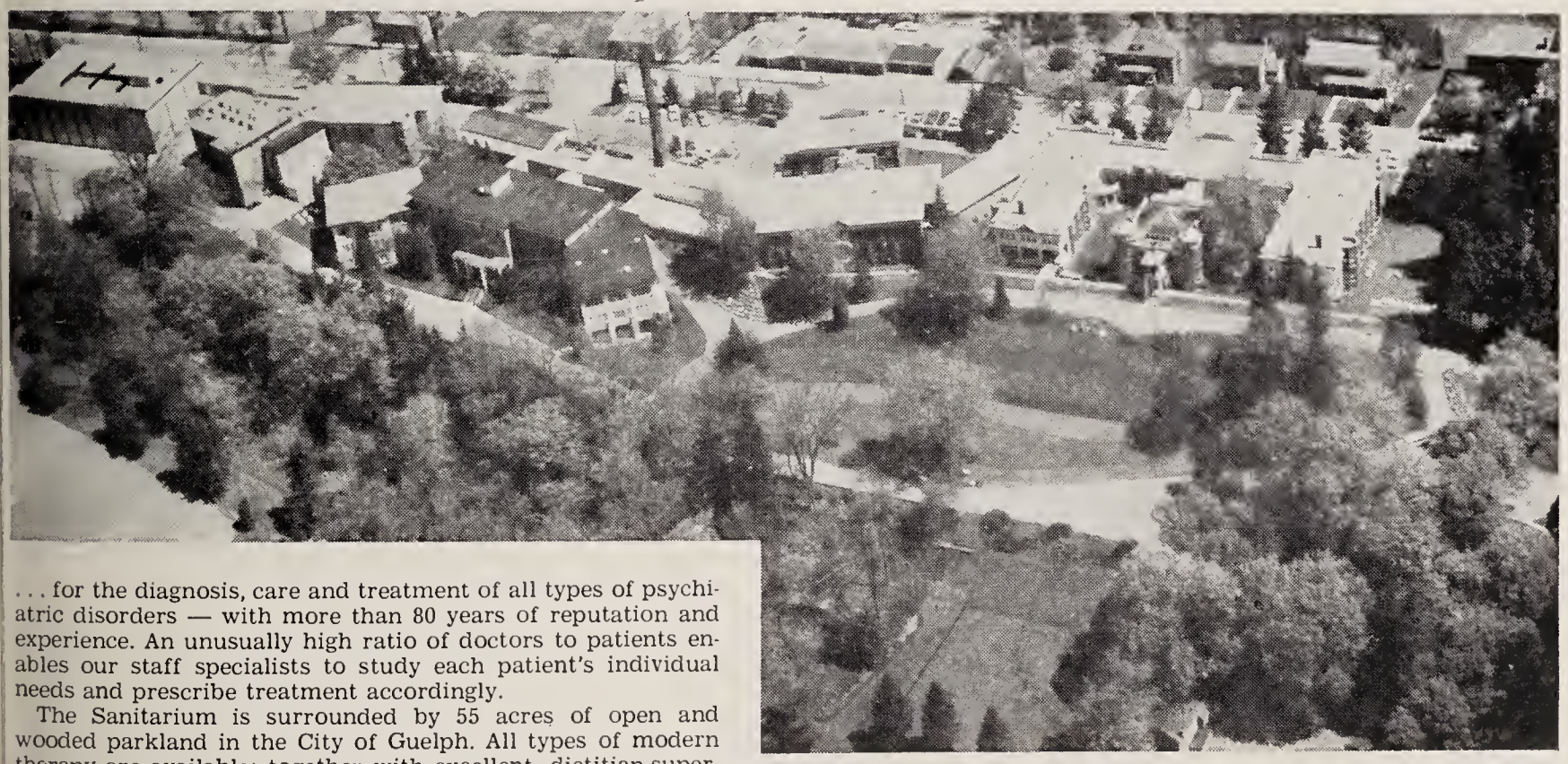

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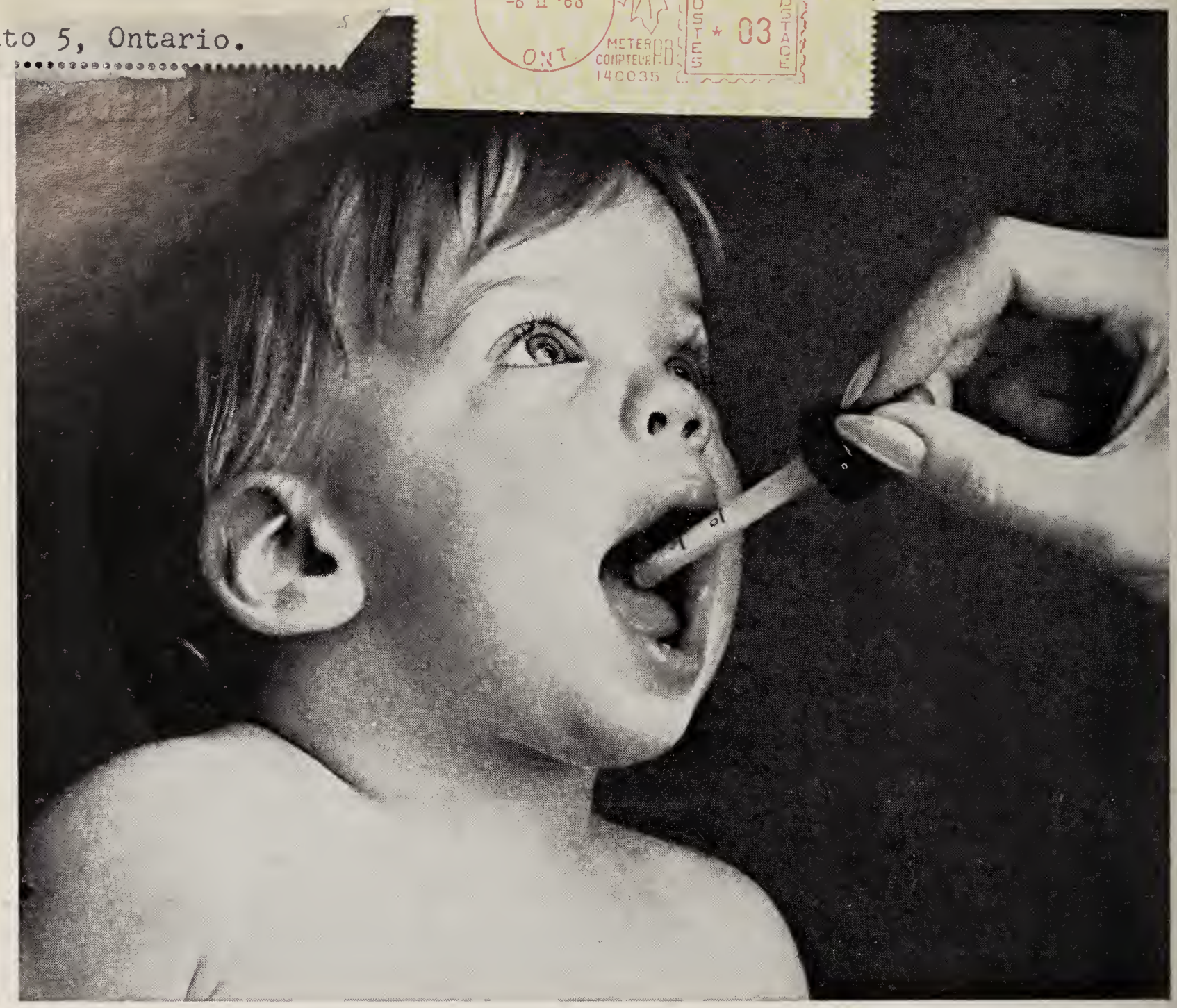

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